FEB 13 1923 ©CIB570022

FEB 13 1923

American Journal of Diseases of Children

VOL. 25 FEBRUARY, 1923 NO. 2

THE INFLUENCE OF GROWTH ON THE BASAL METABOLISM OF CHILDREN*

G. B. FLEMING, B.A., M.D.

GLASGOW, SCOTLAND

The total metabolism of the growing child is universally admitted to be proportionately higher than that of the adult, and Benedict and Talbot[1] have shown that the basal metabolism is also considerably raised during the growth period. From their numerous observations it has been possible for them to provide us with figures showing the expected basal metabolism for any age. Although the basal metabolism for any age is fairly constant, it is probable that the difference between the basal and total metabolism varies considerably in different persons. This variation is probably due to differences of temperament and environment. The active, highly strung boy has a higher metabolism than the lethargic boy. In considering the total food requirements two other factors have to be included. These are: (1) the energy lost in the excreta (feces and urine). In neither of these excreta has complete combustion taken place, and they contain a certain caloric value. The amount lost by this means is about 10 per cent. of the total requirements. (2) The energy expended in growth.

Both Talbot[2] and Holt[3] allow during the first year of life, in addition to the basal requirements, about 45 calories per kilogram for growth; but this seems to be far too much. It must be remembered that the subject while in the respiratory chamber or calorimeter is, as far as we know, growing just as much as when he is lying in bed, consequently, when apportioning the difference in calories between the total and basal requirements, the heat expended in manufacturing new tissue is included in the basal heat output, and only the amount of tissue actually added to the body in growth has to be included under the growth heading.

In the first six months of life a normal infant doubles its weight. Presuming the proportionate composition of its body to be the same at

* Received for publication, Dec. 1, 1922.

* From the Royal Hospital for Sick Children.

1. Benedict and Talbot: Carnegie Institute of Washington Publications, Washington, D. C., 1914, 1921.

2. Talbot, F. B.: Woman's Milk, Am. J. Dis. Child. **18**:229 (Sept.) 1919.

3. Holt, L. E., and Fales, H. L.: Food Requirements of Children, Am. J. Dis. Child. **21**:1 (Jan.) 1921.

birth as it is at 6 months, then the total number of calories added to its body in six months will be equal to the caloric value of the new-born child. From the analyses made by Camerer and Soldner [4] of new-born infants I have calculated that at birth an infant's body has a caloric value of approximately 5,000. If it doubles its weight in six months, then it will have added to its body tissue a value of 5,000 calories, that is, about 27 calories a day and an average of about 5 calories a day per kilogram, taking its mean weight during the first six months of life to be 5 kilograms. It is, therefore, only this amount of the surplus requirements above the basal which can be accounted for by growth.

These considerations show that the basal metabolism during the growth period represents not only the energy expended in carrying on the ordinary vital processes during repose but also a certain quota expended in manufacturing new tissue. Is it possible that the high basal metabolism of this period can be accounted for by this? Unfortunately, two other factors confound the issue. In children under 3 years of age, it is impossible to estimate the basal metabolism in the post-absorptive state, consequently the specific dynamic action of the food exalts the basal metabolism rate to some extent, probably not more than 10 per cent. Secondly, in children there is a much greater proportionate body surface than in adults. This, according to Rubner's law, should cause an increase in the metabolism when compared to body weight. But Benedict and Talbot [1] have shown that the metabolism of the child does not obey Rubner's law, and from their figures it is clear that the high basal metabolism cannot be caused entirely by relatively increased body surface. It seems probable that neither of these two factors can account for the entire increase in basal metabolism, and probably the energy expended in making new tissue plays an important part.

Wilson [5] and Rubner [6] agree that for a lower animal to construct 1 kilogram of normal body substance, it requires an ingestion of about 4,700 calories in food, and Rubner states that for man six times this amount is necessary. That is to say, for a child to add 1 kilogram to its weight 28,200 calories are required and to add 3.5 kilograms, which it does in six months, 98,700 calories are necessary; that is, an average of 548 calories per day. Rubner also considers that in the growing human being 5.2 per cent. of the calories in the diet is retained in the form of new tissue. That is an average of 27 calories per day during the first half year of life.

---

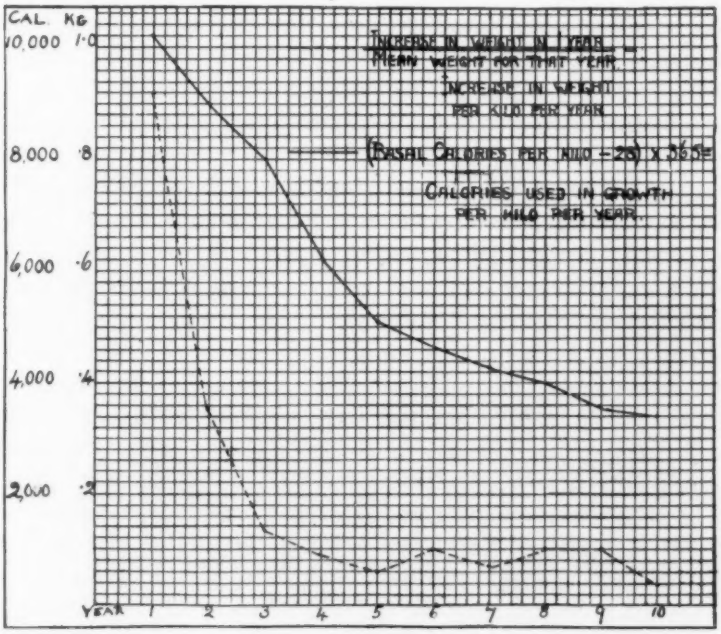
4. Camerer and Soldner, quoted by von Noorden: Metabolism and Practical Medicine, London, W. Heinemann, 1907.

5. Wilson, cited by Lusk: The Science of Nutrition, Philadelphia, 1919.

6. Rubner: Das Problem der Lebensdauer und Seiner Beziehung zu Wachstum und Ernährung, München, 1908.

Unfortunately, neither the calculations of Wilson nor those of Rubner help us to determine how much of the basal heat output is devoted to the manufacture of new tissue for, as explained above, it is probably from the basal heat output that this energy is derived.

We know, however, that in the adult the basal metabolism is about 28 calories per kilogram. Is it possible that in the child the excess over this figure can be accounted for largely by the work done in manufacturing new tissue? The specific dynamic action of food and the relatively large surface area of the child no doubt complicate the proposition, and on account of this it does not seem possible to say definitely how much energy is expended in growth.


CAL. KG
10,000 1·0
8,000 ·8
6,000 ·6
4,000 ·4
2,000 ·2
YEAR 1 2 3 4 5 6 7 8 9 10
INCREASE IN WEIGHT IN 1 YEAR / MEAN WEIGHT FOR THAT YEAR = INCREASE IN WEIGHT PER KILO PER YEAR.
(BASAL CALORIES PER KILO − 28) × 365 = CALORIES USED IN GROWTH PER KILO PER YEAR.

Yearly increase in weight of a normal child per kilogram for the first ten years of life.

The accompanying chart shows the yearly increase in weight of a normal child per kilogram for the first ten years of life $\left(\frac{\text{increase in weight for one year}}{\text{mean weight for that year}}\right)$ and the daily basal metabolism per kilogram minus 28 and multiplied by 365 for each year of life up to 10 years of age. Then, 28 is subtracted from the daily basal metabolism per kilogram, as 28 calories may be taken as the basal figure for adults, and the total basal heat output of a child per kilogram per day minus 28 will give the number of calories per day, and multiplied by 365 will give the number per year that we wish to account for.

Though these two curves do not correspond very closely, especially in the first two years of life, they both show the same tendency to flatten out as age increases and the rate of growth decreases, and seem to afford a certain amount of evidence in favor of the suggestion that the high basal metabolism of the growing child may to some extent be accounted for by the amount of energy expended in the manufacture of new tissue.

NEUROPSYCHIATRIC SEQUELAE OF ACUTE EPIDEMIC ENCEPHALITIS IN CHILDREN *

FRANKLIN G. EBAUGH, A.B., M.D.
Director of the Neuropsychiatric Department of the Philadelphia General Hospital
PHILADELPHIA

In reviewing the enormous number of articles on all phases of acute epidemic encephalitis one cannot help being impressed by the lack of attention paid to children who have suffered from this disease. This is especially true of the important neuropsychiatric sequelae. Few articles deal exclusively with acute epidemic encephalitis in children. Happ and Blackfan,[1] Happ and Mason,[2] Grossman,[3] Leahly and Sands,[4] and recently Hohman [5] have written on this subject, the two last named having confined their remarks to the psychiatric manifestations of this interesting and protean disease.

During the past few months seventeen patients have been referred to the neuropsychiatric clinic for examination, because of marked behavior abnormalities. Many of these patients were referred directly by the school authorities because they had been unmanageable and unable to progress in school. Frequently, they had disturbed the whole class, since they were very quarrelsome and impulsive and often left the school building during class exercises. Nor did these children respond to discipline. Other children were referred by their parents with complaints of equally serious character. In two cases marked sexual precocity was exhibited. In another case, the patient attempted to kill other members of his family. Other children were brought to the clinic for follow-up care after the acute manifestations of the disease had terminated in the hospital. These cases gave us additional opportunity to study the whole course of the disease, especially the neuropsychiatric sequelae.

---

* Read before the New England, New York and Philadelphia pediatric societies, Nov. 4, 1922.
* Received for publication, Nov. 19, 1922.
* From the Neuropsychiatric Clinic, Philadelphia General Hospital.

1. Happ, W. M., and Blackfan, K. D.: Insomnia Following Acute Epidemic (Lethargic) Encephalitis in Children, J. A. M. A. **75**:1337 (Nov.) 1920.
2. Happ, W. M., and Mason, V. R.: Epidemic Encephalitis, Bull. Johns Hopkins Hosp. **32**:137 (May) 1921.
3. Grossman, M.: Late Results in Epidemic Encephalitis, Arch. Neurol. & Psychiat. **5**:580 (May) 1921.
4. Leahly, S. R., and Sands, I. J.: Mental Disturbances in Children Following Epidemic Encephalitis, J. A. M. A. **76**:373 (Feb. 5) 1921.
5. Hohman, L. B.: Postencephalitic Behavior Disorders in Children, Bull. Johns Hopkins Hosp. **33**:120 (Oct.) 1922.

This group consisted of six girls and eleven boys. The age varied from 2 to 14 years. The lapse of time since the subsidence of the acute symptoms of encephalitis is as follows: in four cases, three or more years; in two cases, two or more years; in five cases, from one to two years; and in seven cases, less than one year.

PSYCHIATRIC SEQUELAE

The psychiatric sequelae consist mainly of the following psychopathologic trends:

Total Change in the Patient's Character and Disposition.[6]—This was present in ten of the children (Cases 2, 3, 4, 5, 10, 12, 13, 14, 15 and 16). Normal children who were well adjusted in school and home changed abruptly to a state of hyperkinesis, characterized by transient periods of talkativeness, tension states and emotional outbreaks often leading to general incorrigibility and inability to remain in school. These children were uniformly restless and overexpressive in their activities. They showed marked emotional lability consisting of capricious moodiness, irritability and affability, leading to quarrelsomeness and often overaffectionateness. These behavior trends appeared to be fairly constant in these cases. Owing to their behavior abnormalities it was necessary to keep these ten children out of school. Three of them required prolonged hospital stay during their periods of excitement. One of these patients, a girl, aged 10, was difficult to manage. She was noisy, abusive to other children and capriciously depressed. She was "bossy," quick tempered, and impulsive and showed little respect for authority. This patient was also overaffectionate and before admission to the hospital had accosted men on the streets. She gave evidence of definite sexual precocity. One boy had streaks of cruelty, and on one occasion stabbed a schoolmate with a knife. Another boy, who formerly had been quiet and orderly, became obscene and masturbated in public. He was silly and sang love songs for prolonged intervals. The acuteness of this behavior change necessitated his admission to the psychopathic ward.

In the remaining seven children there was not an abrupt change in character. Some gave a history of previous behavior difficulties, probably due to lack of careful home training regarding habit formation. Two of the six children already had a record of incorrigibility. Another child gave evidence of an hysterical make-up and reacted to unpleasant situations by developing many complaints. For example, he became deaf when told to do anything unpleasant. One boy, previously difficult to manage at home, had sudden outbreaks of violence and on one occasion attempted to kill his sister. He also showed sexual precocity.

6. Francioni, R.: Changes in Character and Mind After Epidemic Encephalitis, Policlinico **28**:575 (April) 1921.

He frequently kissed girls whom he met on the street and on one occasion attempted intercourse. He became vagrant and went to sleep on doorsteps in the early morning hours after walking the streets all night. In each of these children the sequels of the disease consisted in a marked accentuation of their former behavior abnormalities. Three patients did not show any behavior abnormalities after the acute disease terminated.

Nocturnal Restlessness and Insomnia.—Insomnia following encephalitis in children has been a fairly constant finding. This inability to sleep until the early morning hours, often as late as from 3 to 5 o'clock, is followed by sleep into the forenoon. The insomnia is accompanied by motor restlessness. One boy spent many hours talking, singing, whistling, thrashing about in his bed, and fighting with his pillow. It is of interest to note that persistent insomnia rarely occurs in children suffering from other diseases. It is usually seen after an acute infectious disease and occurs in severe types of chorea. Insomnia is one manifestation of a neurotic condition in a child. I agree with the observation of Happ, Blackfan and others,[7] that insomnia is a common sequela of acute encephalitis in children.

Affective Disorders.—Affective disorders have already been referred to as an important part of the change in disposition occurring in children after the acute stage of the disease has terminated. Of three children who showed depressive tendencies, one boy attempted suicide by drowning, while another boy stated that he "was no good" and threatened to kill himself with a gun. He spoke of feeling "heavy hearted." Another boy attempted suicide by choking himself with a handkerchief while in the psychopathic ward. In each case there was no real desire to commit suicide. The affect change was not clear cut and decisive as is the rule in depressive reactions, nor was there the characteristic slowness of thinking and planning. Hohman [8] has previously noted similar findings in adults, in whom the affective changes occur more frequently than in children. The emotional instability present in the other cases under consideration is analogous to that seen in organic reactions.

Hysterical Reactions.—In three of our patients marked hysterical phenomena were observed. One child developed spells of the functional variety, usually to escape from a difficult situation. The spells consisted of prolonged periods of rapid respirations, the child thus feigning illness in order to stay out of school. There was no history of hysterical make-up before this boy developed encephalitis. Another boy developed

7. Naville, F.: The Mental Complications and Sequelae of Acute Epidemic Encephalitis, Encéphalé **17**:423 (July) 1922. Rütimeyer, W.: Postencephalitic Insomnia, Schweiz. med. Wchnschr. **51**:7 (Jan. 6) 1921.

8. Hohman, L. B.: Epidemic Encephalitis (Lethargic Encephalitis), Arch. Neurol. & Psychiat. **6**:295 (Sept.) 1921.

FINDINGS IN ENCEPHALITIS CASES *

Name	Age	Onset	Symptoms	Psychiatric Sequelae	Neurologic Sequelae	Results
1 Maud N.	12	Sept., 1919	Influenza, headaches, dizziness, diplopia, insomnia, ptosis	Nocturnal restlessness, increase in activity during daytime	Choreiform movements.....	Improving, now attends school; choreiform movements disappeared
2 Jessie M.	10	Feb., 1919	Fever; acute delirium; lethargy 3 weeks; visual disturbances	Restless, overactive, incorrigible, sexual precocity	Choreiform movements; endocrine disturbance of hypopituitary type	No improvement
3 Edith S.	6	Jan., 1919	Influenza, delirium; lethargy 5 days	Mental deficiency; imbecility; agitated, restless	Twitchings during sleep	No improvement; no signs of mental development since onset
4 Nathan D.	10	April, 1920	Acute delirium; diplopia; facial twitching; insomnia	Total change in disposition and character, noisy, abusive, destructive, impulsive, untruthful, hysterical attacks, threatened suicide; odd behavior (begs on street); many fears; tics	Irregular respiratory movements; internal strabismus; oversalivation	No improvement; taken from school; admitted to psychopathic ward
5 George McK.	6	Nov., 1920	Fever, jaundice, delirium; lethargy; twitchings	Extreme overactivity, especially nocturnal, with insomnia; became obscene, destructive, unmanageable	Internal strabismus	Improving
6 Peter A.	13	Feb., 1921	Acute delirium, headaches, diplopia	Always incorrigible; extreme insomnia, irritability, impulsiveness, quarrelsomeness; depressive reaction; attempted, 12/1921, to drown himself; hysterical outbreaks; behavior abnormalities contributed to commitment to reform school	Sluggish irregular pupils; internal strabismus; marked salivation	Transient improvement following spinal drainage; incorrigibility decreasing and insomnia decreasing
7 George B.	10	Feb., 1921	Headaches, convulsions; delirium; diplopia short period; lethargy	Periods of excitement; attempted to jump from window; streaks of cruelty; tried to stab another boy; bossy, domineering; increased hysterical tendencies	Oversalivation; irregular pupils	Slow improvement, still unstable
8 Victor La M.	8	Jan., 1921	Headaches, diplopia, delirium; prolonged lethargic period	Incorrigibility before illness showed marked increase; overactive, quarrelsome, antagonistic; attempted to kill brothers and sisters; impulsive; kisses girls on street; vagrant; sexual precocity leading to court commitment	None	Normal behavior during hospital residence; home conditions bad; change in environment and occupational therapy have helped

9 Warren S.	8	June, 1921	Headaches; shooting pains of arms and legs; twitchings; diplopia; delirium; choreiform movements	No behavior abnormalities.....	Choreo-athetoid movements of left arm; typical chorea of left arm and leg; oversalivation; left side facial weakness, mask-like expression; rigidity of left side body	Not seen after discharge from hospital; relative reports improvement after osteopathy
10 Dora O.	10	Feb., 1921	Acute illness followed by lethargic condition 16 days	Numerous behavior abnormalities, marked hyperkinesis leading to general incorrigibility; precocious sex characteristics; vagrancy; placed in O.B. class	None	Doubtful improvement; behavior abnormalities continue; no improvement after hospital care
11 John R.	8	June, 1922	Convulsion, fever; twitching; spinal fluid findings positive; insomnia, nocturnal restlessness	No behavior abnormalities after acute illness cleared up	Bilateral twitching of temporal muscle; oversalivation	Well; improvement after spinal drainage
12 Sophia J.	8	March, 1922	Dizziness, headaches, earache; delirium; lethargy 2 weeks duration	Manic-like reaction, continuously wandered about room; overaffectionate	Weakness, right external rectus; nystagmoid movements; ptosis; facial weakness on left side	Continued incorrigibility; taken from school
13 Ernest S.	13	May, 1922	Marked abdominal pain, headache; lethargy 1 week	Became silly, obscene, masturbated in public; vagrant; many fears	Mild optic neuroretinitis	Return to school; improving; spinal drainage a factor
14 George McD.	8	March, 1922	Ptosis, diplopia, delirium, insomnia	Odd antics at night, fights with pillows for prolonged intervals; sleeps till noon; overactive	Irregular pupils; left internal strabismus; occasional choreiform movements	Little improvement; insomnia; medication; hydrotherapy ineffectual
15 Charles K.	14	Feb., 1922	Headaches, dizziness, radiculitis, diplopia, masseter tenderness, nocturnal restlessness	Threatened suicide because of "heavy heartedness"; insomnia; frequent masturbation	Frequent headaches	Marked improvement after spinal drainage; working (bell boy)
16 Dorris F.	2	April, 1922	Acute illness characterized by eyes crossing and total absense of mental development since	Overactive, irritable, whiny, fussy; typical picture of idiot; normal development before	Strabismus, choreiform movement of both arms; movement of head	Evidently permanent sequelae
17 Isadore L.	3½	Feb., 1919	Normal birth, slept continually for 8 days; on being fed, immediately fell asleep, followed by inability to sleep for 11 weeks; cried continually; has shown no mental development since; mother had influenza in middle pregnancy, other siblings normal except one, who evidently had a meningitis during infancy followed by mental retardation	No evidence of mongolianism.....	Typical idiocy	If encephalitis, belongs to permanent mental deficiency residual

* Cases are presented in schematic form to show symptoms, onset, psychiatric and neurologic sequelae, as well as the present condition of the patient. In all cases, a diagnosis of "encephalitis" was made by exclusion. Wassermann reactions, as well as other laboratory reports, were negative in all cases unless noted.

spells of screaming and yelling to avoid the discipline of a correctional school. Another boy, previous to the attack of encephalitis, had shown hysterical tendencies. He had spells of blindness, deafness, and aphonia when he wished to dodge unpleasant duties. These tendencies were all more marked and troublesome as sequelae of his attack of encephalitis.

Tics.—Irregular movements of the head or of one extremity, sniffing of the nose, clicking of the tongue, biting the finger nails and obsessive spitting have been observed in these cases. These tics are considered to be of organic origin following encephalitis.

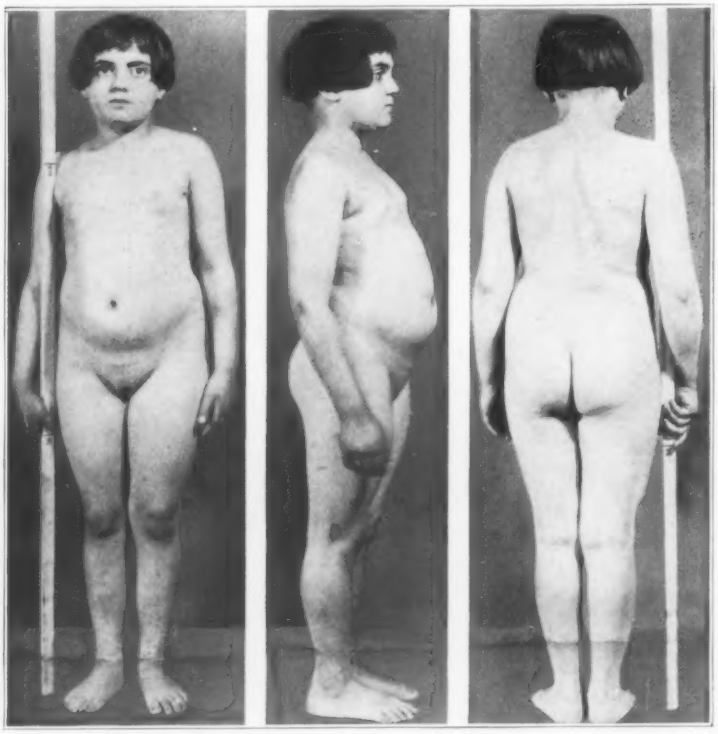


Fig. 1 (Case 2).—Anterior, lateral and posterior views of patient that had suffered an attack of encephalitis in February, 1919, which was followed by evidence of endocrine disturbance of a hypopituitary type. The illustrations show the distribution of the fat. Laboratory reports revealed increased sugar tolerance; basal metabolism, 16 per cent. above normal. The sella turcica was normal.

Mental Deficiency.[9]—We have found mental deficiency to be one of the sequelae especially to be considered, if encephalitis occurs during

9. Paterson, D., and Spence, J. C.: The After-Effects of Epidemic Encephalitis in Children, Lancet **2**:491 (Sept. 3) 1921.

infancy. Cases 3, 16 and 17 belong in this class. Two of these patients developed the disease at the age of 2 years. One of the two is now 6 years of age, but her mental age, determined by the routine psychologic examination, remains 2 years. Previous to her acute illness she showed normal mental development. One infant evidently had encephalitis at birth. Two years later she presented the picture of an idiot. The evidence in this case, as in the cases reported by Jorge and Mercier,[10] suggests that congenital encephalitis occurs.

NEUROLOGIC SEQUELAE

The neurologic sequelae can briefly be referred to as, first, subjective complaints, and secondly, objective manifestations. Headaches, dizziness, diplopia, drowsiness during the daytime, and asthenia constitute the main subjective symptoms. Oversalivation also was present and was a troublesome factor in a large percentage of our cases.

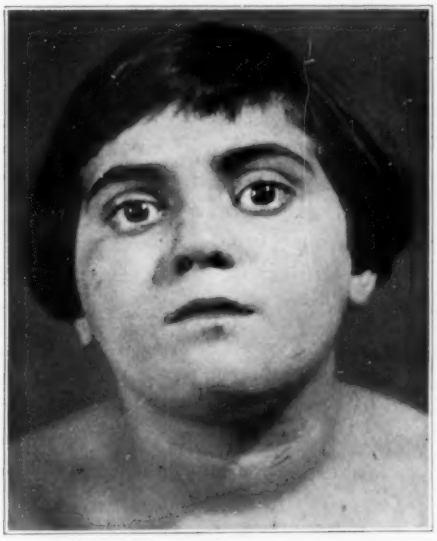


Fig. 2 (Case 2).—Appearance of patient, showing tendency to exophthalmos which may indicate thyroid activity to compensate for hypopituitarism; also showing residual left-sided ptosis.

Disturbance of Motility.—This was a very common finding. It consisted of choreiform and all types of incoordinated movements which occurred for prolonged periods in seven cases (Cases 1, 2, 3, 9, 12, 14

10. Jorge, R.: Epidemic Encephalitis and Pregnancy. Transmission of the Disease by the Mother to the Fetus, Paris méd. **2**:454, 1921. Mercier, R.: Placental Transmission of Epidemic Encephalitis, Bull. de l'acad. de méd. **85**:625 (May 31) 1921.

and 16). It is interesting to note that these disturbances in motility were apparently related to the behavior and emotional changes mentioned above. I say this because emotional stimuli brought on the irregular, incoordinated movements. These movements frequently occurred during sleep and were not for the most part accompanied by pain. Radiculitis of a severe type was present in only one case, and in this child we found also choreo-athetoid movements. Tremors were frequent, though not especially characteristic.

Visual Disturbance.—Weakness or paralysis of one rectus muscle was observed in seven cases (Cases 1, 2, 5, 6, 12, 14 and 16). The sixth nerve was the one most frequently affected. Ptosis of a marked degree was not present. It was noted in two cases as a permanent finding (Cases 2 and 14). Eye ground examinations were negative with one exception in which there was a mild degree of optic neuroretinitis present for a short period. Many children complained of difficulty in reading. The visual defects of some improved after appropriate lenses were fitted.

Other Neurologic Findings.—Facial weakness was observed in only two cases. Evidence of pyramidal and extrapyramidal tract involvement was noted in one child. Involvement of the corpus striatum was considered to be present in this case which accounted for a rigidity of one side of the body and immobile facies. No other patient in this series showed any evidence of a paralysis agitans syndrome.

Disturbances of the autonomic system consisting of oversalivation, and vasomotor symptoms were present. Exophthalmos developed in one child as a sequela of the disease.

Endocrine Findings.—One case showed the characteristic findings of hypopituitarism, and obesity was a development in several patients (Figs. 1 and 2). States of undernutrition have also occurred.

PROGNOSIS

The prognosis of acute epidemic encephalitis in children should be made very conservatively. I do not wish, however, to give a pessimistic outlook. In this series of seventeen patients, five (Cases 1, 11, 13, 14 and 15) have been progressively improving, and eventual recovery without a permanent residual pathologic condition is expected. Four others are improving slowly (Cases 5, 6, 7 and 9), although the ultimate outlook remains doubtful. The remaining eight children seem to be unimproved, three of them appearing to be permanently mentally deficient. Improvement, therefore, and possibly complete adjustment are to be expected in approximately half of these cases. A period of five years should be allowed to determine the permanency of the neuropsychiatric sequelae.

TREATMENT

There is no specific treatment for encephalitis. Medicine, as is usual in organic cases, has been of no avail. Routine sedatives and hypnotics have not produced sleep. Continuous warm baths have been of use in some cases during periods of excitement. Spinal drainage has given conflicting results. In four cases, however, there appeared to be transient improvement following this procedure. One child apparently was made worse. Psychotherapy has been disappointing in this application. Occupational therapy has proved to be of value. A prolonged period of observation and treatment in the hospital ward appears advisable, especially since this creates a new environment for the patient, which may be helpful. This constitutes one of the aspects of the universal need for a children's psychopathic ward. In a few cases, commitment may be indicated. These patients did not react well to discipline. However, a well regulated home routine and discipline were advised, especially for patients showing hysterical tendencies.

SUMMARY

In the seventeen cases of postencephalitis disturbances of a neuropsychiatric type the psychiatric sequelae consisted of: (1) total change in character and disposition with characteristic hyperkinetic states, leading to behavior oddities consisting of emotional lability, sexual precocity, general incorrigibility, etc.; (2) insomnia with nocturnal agitation; (3) affective disorder of a depressive type; (4) hysterical reactions; (5) tics, fears, and (6) mental deficiency.

Neurologic sequelae consisted of headaches, dizziness, diplopia, drowsiness, asthenia and oversalivation. Disturbances in motility, especially choreiform movements, were present. These disturbances appear to be related to the mental state. Visual disturbance and facial weakness also occurred as residuals. Evidence of endocrine change was noted in one case.

The prognosis should be guarded; but pessimism should be avoided. Fifty per cent. of these patients are well or improving.

There is no specific treatment for these conditions. Children should be sent to psychopathic wards for observation. Spinal drainage was effectual in several cases. These children do not react to discipline.

ACUTE HEMORRHAGIC ENCEPHALITIS

REPORT OF A CASE FOLLOWING SCARLET FEVER *

JOHN A. TOOMEY, M.D.; LEON H. DEMBO, M.D.,
AND
GUTHRIE McCONNELL, M.D.
CLEVELAND

The comparative infrequency of acute hemorrhagic encephalitis as a sequela of scarlet fever, the clinical picture presented, and the unusually rapid course of the case here recorded, with fatal termination, are points of sufficient interest to justify a rather detailed report.

REPORT OF CASE

History.—E. G., boy, white, aged 6 years, was admitted, July 31, 1922, suffering from convulsions. The mother stated that until three days previously he had apparently been in good health since he had had scarlet fever. He had been active in play, and had made no complaint. July 28 he complained of sore eyes, avoided light, and had some apparent stiffness of the right leg. A physician was summoned, and, following treatment, there was some improvement. The next day he vomited everything taken by mouth, was feverish, and the mother noted that he seemed drowsy and had a squint. At this time there was rigidity of the right leg. He was much worse on the following day, the lethargy increasing and the vomiting becoming more marked. He could, however, be aroused. That evening he began to have convulsions which started with twitching of the fingers and finally became generalized. A lumbar puncture was done by the physician in attendance, and bloody fluid was withdrawn, which was attributed to faulty technic. The convulsions persisted, and there was involuntary evacuation of the bowels and bladder. The boy was placed in hot packs, but the convulsions continued, lasting from one half to one hour. The patient rapidly lapsed into coma and was sent to the contagious division of the City Hospital, July 31, at 11 a. m.

The father and mother of the boy were living and well. One brother, aged 11, was living and well. The mother had never had any miscarriages, and there was no history of cancer or tuberculosis in the family.

The child had measles at 7 months, chickenpox at 4 years, and he had had frequent attacks of sore throat, especially during the winter months. He had been breast fed until the age of 11 months. Congenital clubbed feet were corrected during the first two years. He had always been a robust child and had never had any serious illness. July 7 the mother noticed that he seemed to have some fever. He was put to bed, and a physician, who was called, stated that the child looked as if he were going to have an attack of one of the acute exanthems. The next day a typical scarlatiniform rash appeared. The child remained in bed for the following three days and was then allowed to be up without the permission of the attending physician. He seemed to be getting along fairly well, and during the next three weeks played as usual. July 28 the present illness began with the complaint of sore eyes and drowsiness.

Physical Examination.—On admission he was comatose, and was having frequent convulsions. He was well developed and well nourished. Cyanosis was well

* Received for publication Dec. 12, 1922.

* From the Departments of Pathology and Pediatrics, Western Reserve University, and the Division of Contagious Diseases, City Hospital.

marked, and respirations were of the Cheyne-Stokes type. There was marked rigidity of the arms and legs. The head presented no abnormalities. The eyes were fixed and staring, and the pupils were contracted to almost pin points and not reacting. The ears and nose were negative. The lips were cyanotic, the mouth was open, and the tongue protruded slightly; the teeth were negative. There was some rigidity of the neck. The thorax was well developed, symmetrical and presented no bony abnormalities. The respirations were shallow. Moist râles were heard throughout the chest. Percussion revealed nothing remarkable. The heart beats were rapid and regular; the sounds were heard well and were of good muscular quality. There were no murmurs, and there was no apparent enlargement. The abdomen was well rounded, somewhat rigid, but moving with respiration. No masses were palpable. The extremities were cyanotic, especially the legs. The skin was hot, dry and cyanotic. The temperature on admission was 40.4 C. The pulse was rapid, bounding and of alternating volume.

Fig. 1.—Transverse section through midbrain showing hemorrhage of the ventricular floor.

Diagnosis.—From the past history of scarlet fever and the character of the onset of the present illness, a diagnosis of nephritis with uremia was made. Because of the serious condition of the child a detailed examination could not be made.

Treatment.—The boy was immediately placed in a hot pack and given stimulation by the hypodermic route. Rectal injections of chloral and bromids were given to control the convulsions. When he was being removed from the pack, respirations ceased, and, in spite of artificial respiration and circulatory stimulation, death ensued. The entire course from the time of admission to death was not more than forty-five minutes in duration.

Necropsy Report.—The body is that of a well developed, well nourished white male child, aged 6 years.

Head: There are no abnormalities of the scalp, calvarium or meninges. The brain weighs 1,430 gm. and presents no abnormalities of the external surface.

The ventricles are full of blood and clots. The basal nuclei are hemorrhagic, soft and friable, and, where they are of such consistency that they can still be cut, are filled with many petechiae. Serial section of the brain reveals the more marked destruction of the thalamus on the left side than on the right. The superficial portions are necrotic and hemorrhagic. Beneath this area there is a zone of pinpoint hemorrhages. On the right side the hemorrhage has taken place in the subependymal tissues.

Peritoneal Cavity: The peritoneum is smooth and glistening. There are no adhesions present and no fluid. The appendix is retrocecal and bound down by adhesions. The thoracic viscera show no gross abnormalities. The pericardial cavity shows a smooth and glistening lining, with no excess of fluid. The mucosa is pale and of normal thickness. The endocardium is smooth and glistening throughout, except for several pinpoint to pinhead petechiae found in the left ventricle. The valves are entirely normal.

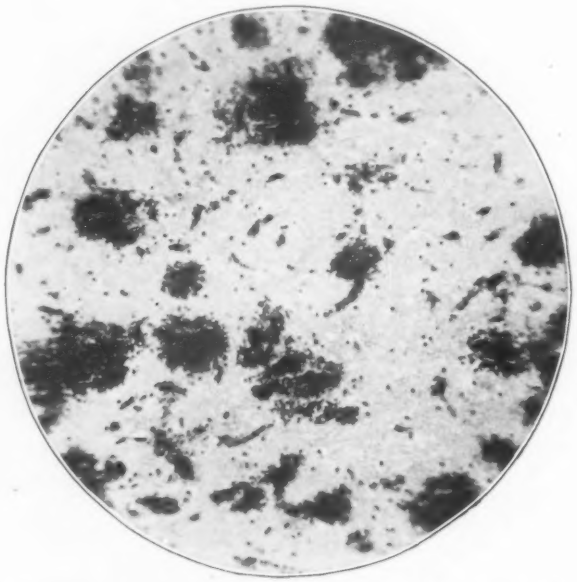


Fig. 2.—Section showing multiple hemorrhages in the brain tissue.

Lungs: The external surfaces are smooth, shiny and bright red. Crepitation is present throughout. On section the tissue is bright red. There is no excess of fluid and no consolidation. The bronchi are slightly congested. The aorta is smooth, glistening and elastic throughout. The spleen is enlarged and the capsule smooth. It is a pale brick red, and on section it is a pale, bluish red, the malpighian bodies and trabeculae being normally prominent. The organ is not friable. The suprarenals show no gross abnormalities.

Kidneys: The capsules strip with ease. The surfaces are smooth, and, on section, they do not bulge. The cortices are regular and the striations well marked. The right kidney is congested, the pyramids being of a purplish color. The left kidney is pale. There are no abnormalities of the pelves of the ureters.

Liver: The liver is normal in shape and consistency. The capsule is smooth and a brownish red with yellow mottling. The architecture is well preserved. The gallbladder contains a small amount of dark, viscid bile. There are no gross abnormalities.

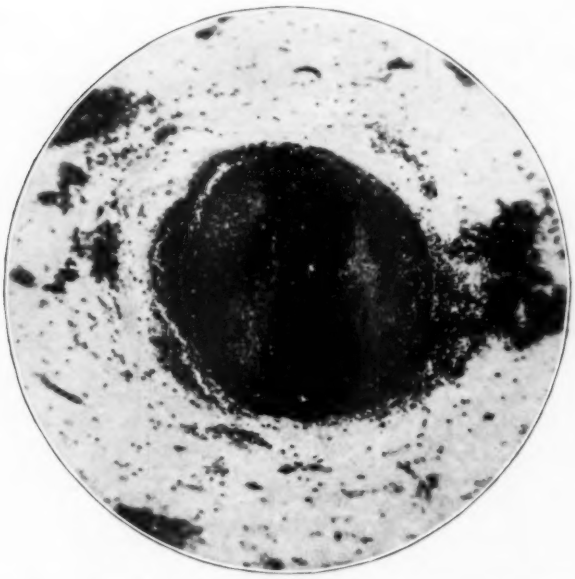


Fig. 3.—Section showing thrombosis of cerebral vessels.

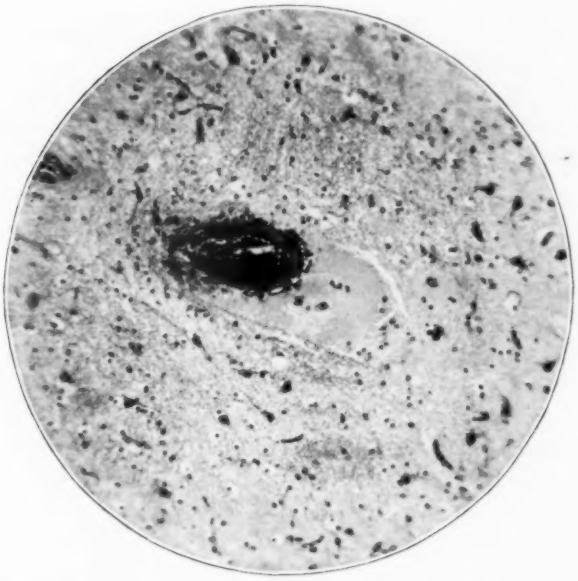


Fig. 4.—Section showing congestion with exudation in the perivascular lymph spaces.

Stomach: The stomach contains a small amount of digested food. The mucosa is smooth and white. The duodenum, pancreas, small and large intestines, bladder and prostate are normal. The thymus is about the size of a hickory nut and is soft and vascular.

Anatomic Diagnosis.—Edema of the brain; acute hemorrhagic softening of the basal nuclei, with intraventricular hemorrhages; subendocardial petechiae (left ventricle); congestion of the spleen.

Microscopic Examination.—Heart: There is slight cloudy swelling and vacuolation of muscle fibers. Section of the wall of the left ventricle shows an extensive subendocardial hemorrhage surrounding, and in some instances destroying, the Purkinje cells.

Lungs: Many abnormally large alveoli resulting from the rupture of the alveolar walls are present. There is diffuse congestion and infiltration of the peribronchial tissues by many lymphocytes, with some desquamation of the bronchial epithelium.

Liver: Lobulation is unusually distinct. The portal tissue is well developed, and the liver cells at the periphery of the lobule contain an abnormal amount of a granular, brownish pigment. Sinusoids contain more leukocytes and lymphocytes than is usual. There is some periportal leukocytic infiltration.

Spleen: There is endothelial hyperplasia, but no congestion. The leukocytes are greatly increased in number. The germinal centers are quite distinct.

Pancreas: In a few of the lobules are areas in which the acini are apparently atrophic and the amount of fibrous tissue increased. The suprarenals and the thymus show nothing abnormal.

Brain: Many of the blood vessels are completely occluded by thrombi of recent formation. There is no evidence of cellular proliferation. The walls show degenerative changes and are outlined by deeply staining fragments of broken down nuclei. Many of these thrombosed areas are surrounded by distinct zones of hemorrhage. There are also many apparently isolated areas of hemorrhagic infiltration, varying greatly in extent. In many instances the perivascular lymph spaces are greatly distended by a coagulated exudate. The brain tissue adjacent to these areas is edematous. A few leukocytes are scattered here and there, but no definite leukocytic infiltration is present.

SUMMARY: Thrombosis of cerebral vessels accompanied by edema and hemorrhagic infiltration; pulmonary emphysema; pigmentation of liver; endothelial hyperplasia of the spleen.

COMMENT

A search through the literature reveals some interesting case reports similar to this one in symptomatology, but differing in that many of the patients partially recovered, retaining some degree of paralysis. By far the majority of cases occurred as late sequelae of influenza, although many followed in the wake of other acute infections. Putnam [1] reports a case occurring in a boy, aged 13, following an attack of mumps. The chief symptoms in this case were headache, drowsiness, delirium, numbness of the extremities, a partial ptosis of the eyelids with an internal strabismus of the right eye. These symptoms were followed by deafness, optic neuritis and bulbar symptoms. Oppenheim [2] reports several cases of long duration with partial recovery. In one case, that of a girl, aged 16, the duration was four months, the

1. Putnam, J. J.: J. Nerv. & Ment. Dis. **24**: (Jan.) 1897.
2. Oppenheim, N.: Die Prognose der akuten, nicht-eitrigen Encephalitis, Deutsch. Ztschr. f. Nervenh. **6**:377, 1894.

main symptoms being headache, motor and sensory aphasia, and optic neuritis. In this case the outcome was favorable. Another patient, a girl, aged 10, was stricken three months after a slight attack of influenza. Fever, loss of speech, optic neuritis, prostration, stiffness of the neck muscles and unconsciousness lasting three days characterized the clinical picture in this case. The final outcome in this case was also favorable. Nauwerck's [3] case occurred in a girl, aged 14, during an epidemic of influenza. Remittent fever, convulsions limited to the left side, vomiting, coma and death comprised the notable clinical features. Necropsy revealed the brain to be soft and edematous, with numerous foci of hemorrhagic softening. Fürbringer [4] cites a case following scarlet fever, occurring in the fifth week after the primary illness. Königsdorf [5] and Schmidt [6] described rather typical cases occurring during the epidemic of influenza in 1889-1891. In the latter's case, the patient, a girl, aged 19, was suffering from chlorosis. The clinical picture was characterized by headache, apathy, epileptic seizures and somnolence. Later the breathing became stertorous, the pupils were small and failed to react to light, and there was conjugate deviation. Necropsy revealed hemorrhagic encephalitis, with blood in both lateral ventricles, especially in the left ventricle.

Etiology.—Several theories have been advanced as to the causative factors, chief of which are the bacterial and the toxic. The former supports the hypothesis that this type of encephalitis is due to a direct invasion of the cortex of the brain (Hoppe [7]) by the bacteria which cause the primary disease; the latter attributes the cause to a toxic product of the acute infectious diseases.

Regarding sex, male and female are equally affected. Relative to age, the period of greatest frequency ranges from early childhood to puberty.

Hoppe [7] states that measles is frequently complicated with encephalitis; next in order are typhoid, scarlatina and diphtheria. A characteristic feature of this complication is that it usually occurs during the period of convalescence, or, not infrequently, weeks or months later.

---

3. Nauwerck: Influenza und Encephalitis, Deutsch med. Wchnschr. **21**:393, 1895.

4. Fürbringer, P.: Deutsch med. Wchnschr., 1892, No. 3.

5. Königsdorf: Ein neuer Fall von akuter haemorrhagischer Encephalitis, Deutsch med. Wchnschr. **18**:182, 1892.

6. Schmidt, J.: Akute primäre hemorrhagische Encephalitis, Deutsch. med. Wchnschr. **18**:703, 1892.

7. Hoppe, N. M., in Tice's Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc. **9**, 1920.

Of the cases occurring in adults influenza is the cause in the vast majority. Freyhan [8] states that the main feature is found in the small hemorrhages which come from the dilated and overfilled capillaries.

Trauma is mentioned as a factor. Drinkler [9] described a case occurring in a young child, who, following a severe blow on the head two and a half years before, had developed symptoms characteristic of hemorrhagic encephalitis. Hoppe's [10] case occurred in a boy, following a fall. At necropsy, the brain was seen to contain many hemorrhagic cysts. The influence of trauma may be brought about in a purely mechanical way, combining the factors of concussion and inflammatory reaction followed by softening. Again, a secondary circulatory infection may intervene, causing a localized or circumscribed inflammatory process.

Pathology.—There are two distinct types of acute hemorrhagic encephalitis which differ clinically and pathologically. Under the term "acute hemorrhagic encephalitis" is included the so-called "Strümpell-Leichtenstern" form. This type was first described by Strümpell in his paper on infantile cerebral palsies. The second is the syndrome characterized by multiple hemorrhages occurring most frequently in the cortex, less commonly in the basal ganglions.

The color varies according to whether the hemorrhages are recent or late, the pigment changes being from a purplish brown to a brownish yellow tint. There is dilatation of the arterioles and capillaries and a transudation of red and white blood corpuscles into the surrounding tissue. The ganglionic cells are secondarily affected, the protoplasm undergoing swelling and the nuclei becoming less distinct. In those cases in which the hemorrhagic areas are extensive, involving a large cortical area, the basal nuclei and the walls and floor of the ventricles, the outcome is invariably fatal. In those cases, however, which are less extensive and terminate in recovery, the patient is left with cortical defects resulting from fibrotic changes with the formation of scar tissue. Strümpell's contention was that these scars were the cause of the palsies seen in childhood following an attack of this type of encephalitis.

Occasionally there is cyst formation. Oppenheim stated that this form of encephalitis was frequently associated with sinus thrombosis and thrombosis of the veins in cases in which there was, clinically, a well marked chlorosis.

---

8. Freyhan: Ueber Encephalitis hemorrhagica, Deutsch. med. Wchnschr. **21**:643, 1895.

9. Drinkler, M.: Mitteilung eines tödlich verlaufenen Falles von traumatischer Gehirnerkrankung (allgemeine Unruhe, Schwachsinn, Sprachstörungen, u.s.w.) mit dem anatomischen Befunde einer Polioencephalitis hemorrhagica inferior acuta, Deutsch. Ztschr. f. Nervenh. **6**:465, 1895.

10. Hoppe, H. H.: J. Nerv. & Ment. Dis. **29**:9, 1902.

In Wernicke's syndrome the lesion involves the gray nucleus of the third nerve and the gray matter of the thalamus, with some capillary hemorrhages in the cortex. The essential pathologic processes consist of vascular changes, with hemorrhage and destruction of the gray matter.

Symptomatology.—The clinical manifestations of the Strümpell-Leichtenstern type are many and varied, and, except for those observers who have seen and dealt with a great number of these cases, present no distinctive features. Occurring during an epidemic in which many such cases are prevalent, the symptoms might at once suggest the true condition. In isolated instances, however, as in the case here reported, a clinical diagnosis could hardly be made with certainty, especially since the picture presented a syndrome that might well have been mistaken for uremia.

The onset is usually some time after recovery from one of the acute infectious diseases. There may be some distinct prodromal symptoms, such as headache and malaise. More often the onset is sudden, with headache, fever, restlessness, convulsions, rigidity of the extremities, and a rapidly developing coma. Ocular symptoms are common and are manifested by ptosis, strabismus and inequality of the pupils, with failure to react to light. The respirations are of the Cheyne-Stokes type. In cases terminating in death, the coma increases, and respiratory failure (as in our case) occurs.

The Wernicke type is characterized by marked delirium, paralysis of the external eye muscles, ptosis, strabismus, facial paralysis, constipation, and, not infrequently, vomiting.

Course and Duration.—The course and duration vary, depending on the extent of involvement. In those cases in which the hemorrhagic areas are confined chiefly to the cortex, the disease may run a course of from several days to many weeks, terminating in partial recovery. In fulminating cases, in which the cortex, basal nuclei and walls and floor of the ventricles are involved, death may follow within from twenty-four to forty-eight hours after the onset.

Diagnosis.—A number of conditions must be considered. Cerebral abscess, uremic focal symptoms, thrombosis, and cerebrospinal meningitis are the important conditions entering into the question of diagnosis. The case of Norris [11] illustrates some of the difficulties encountered in the diagnosis of this condition. His patient, a man, aged 28, after returning from the day's work, was found unconscious. There were twitching of the side of the face, a partial paralysis of the right arm and leg, and slight nystagmus. Lumbar puncture revealed a cell count

11. Norris, G. W.: Acute Hemorrhagic Encephalitis, Internat. Clin. **1**:24-28, 1922.

of 1,250, with the fluid under increased pressure. The eyegrounds were negative. There was a paralysis of the right side without spasticity. Positive Babinski and Oppenheim reactions were present, with moderate cervical rigidity. He had been in the hospital three weeks prior to his present admission, suffering from a bilateral lobar pneumonia. On the strength of this history, together with the suggestive physical findings, a diagnosis of meningitis was made, probably pneumococcic. Necropsy revealed the true nature of the condition—an acute hemorrhagic encephalitis.

As stated, when this disease appears as the aftermath of an acute infection, in the absence of an epidemic, the diagnosis is extremely difficult. It is unfortunate that in our case we were unable to make a more thorough examination. The few hurried observations made were scarcely sufficient to present even a clue to the underlying condition.

Treatment.—The treatment is largely symptomatic. The prognosis is at best unfavorable. In some cases in which partial recovery occurs, there is usually some defect either in the form of epileptiform seizures, an obtunded mentality, or some degree of paralysis. Many question the diagnosis in cases in which recoveries are reported.

SUMMARY

1. The fatal case of acute hemorrhagic encephalitis reported was a late sequela of scarlet fever.

2. The hemorrhages found in the brain and the character of the onset and symptoms conform to the description of the Strümpell-Leichtenstern type.

3. The diagnosis is difficult because of the resemblance of this disease to other more common diseases.

4. The prognosis is unfavorable in the majority of cases.

of 1,250, with the fluid under increased pressure. The eyegrounds were negative. There was a paralysis of the right side without spasticity. Positive Babinski and Oppenheim reactions were present, with moderate cervical rigidity. He had been in the hospital three weeks prior to his present admission, suffering from a bilateral lobar pneumonia. On the strength of this history, together with the suggestive physical findings, a diagnosis of meningitis was made, probably pneumococcic. Necropsy revealed the true nature of the condition—an acute hemorrhagic encephalitis.

As stated, when this disease appears as the aftermath of an acute infection, in the absence of an epidemic, the diagnosis is extremely difficult. It is unfortunate that in our case we were unable to make a more thorough examination. The few hurried observations made were scarcely sufficient to present even a clue to the underlying condition.

Treatment.—The treatment is largely symptomatic. The prognosis is at best unfavorable. In some cases in which partial recovery occurs, there is usually some defect either in the form of epileptiform seizures, an obtunded mentality, or some degree of paralysis. Many question the diagnosis in cases in which recoveries are reported.

SUMMARY

1. The fatal case of acute hemorrhagic encephalitis reported was a late sequela of scarlet fever.

2. The hemorrhages found in the brain and the character of the onset and symptoms conform to the description of the Strümpell-Leichtenstern type.

3. The diagnosis is difficult because of the resemblance of this disease to other more common diseases.

4. The prognosis is unfavorable in the majority of cases.

INTRAPERITONEAL TRANSFUSION WITH CITRATED BLOOD

AN EXPERIMENTAL STUDY *

DAVID M. SIPERSTEIN, M.A., M.D.
Fellow in Pediatrics, University of Minnesota
MINNEAPOLIS
AND
J. MARTIN SANSBY, B.S., M.D.
ST. PAUL

Blood transfusion in infants and children is a recognized therapeutic procedure. In the past, the site of transfusion has been limited to the superior longitudinal sinus in the region of the anterior fontanel, or to the direct exposure of some vein, preferably in the elbow.

The anterior fontanel route, popularized by Helmholz [1] in 1915, affords an excellent method in infants in whom this structure is accessible. This approach, however, has its limitations. Fischer,[2] Lowenburg,[3] Unger,[4] and others, have pointed out the dangers inherent in puncturing the superior longitudinal sinus.

In older infants, those more than 18 months of age, the fontanel is not usually patent, and the only other procedure remaining is the exposure of a vein and the injection of the donor's blood. We need not go into a discussion concerning the technical considerations involved in this method. It is conceded that the number of blood transfusions in young children has been influenced markedly by the difficulties encountered.

In view of these existing dangers and limitations, it was thought that another avenue of approach which would be safe, simple to apply, and which would afford fairly rapid results, would be of value. It is the purpose of this paper to outline a method which meets these fundamental requirements.

PROBLEM

The intraperitoneal transfusion of citrated blood offers a feasible and practical solution of this problem. In order to demonstrate the

---

* Received for publication, Nov. 6, 1922.

* From the Department of Pharmacology, University of Minnesota.

1. Helmholz, H. F.: The Longitudinal Sinus as the Place of Preference in Infancy for Intravenous Aspirations and Injections, Including Transfusion, Am. J. Dis. Child. **10**:194 (Sept.) 1915 .

2. Fischer, L.: The Superior Longitudinal Sinus in Infants; Its Value in Transfusion and for Rapid Medication, Med. Rec. **94**:399 (Sept. 7) 1918.

3. Lowenburg, H.: Blood Transfusion via Longitudinal Sinus, with Report of Cases, Therap. Gaz. **44**:381 (June 15) 1920.

4. Unger, L. J.: Transfusion of Unmodified Blood, J. A. M. A. **69**:2159 (Dec. 29) 1917.

utility of this proposed method it is necessary to show: (1) that the red blood cells are absorbed from the peritoneal cavity; (2) that they reenter the blood stream as red blood cells, and (3) that they are capable of functioning after reentering the general circulation.

REVIEW OF LITERATURE

ANIMAL EXPERIMENTS SHOWING ABSORPTION FROM THE PERITONEAL CAVITY

In 1862, von Recklinghausen[5] injected defibrinated blood into the peritoneal cavity of rabbits and found that absorption took place.

Ponfick,[6] in 1875, noticed an increase in red blood cells which reached a maximum in one or two days following the intraperitoneal injection of defibrinated blood.

Bizzozero and Golgi,[7] also working on rabbits, in 1880, reported an increase in hemoglobin following the intraperitoneal injection of defibrinated blood. They were able to note a change in twenty minutes which increased gradually up to the first or second day and persisted for about a week. They found that in anemic rabbits the hemoglobin increased more rapidly, and persisted for a long time (in one case twenty-seven days).

Poncet[8] in 1879, while studying periuterine hematocele experimentally, noticed the constant complete disappearance of the blood injected into the peritoneal cavity.

Arloing and Tripier[9] verified these experiments by connecting the carotid of one animal directly with the peritoneal cavity of another. They found that rapid absorption invariably took place.

In 1880, Obalinski[10] found an increase in red blood cells one hour after the injection of defibrinated blood which persisted for a long time. The greatest increase was 49 per cent., the lowest 12 per cent., independent of the amount of blood injected. He was unable to demonstrate a hemoglobinuria at any time.

During the same year, Foa and Pellacani[11] showed that peritoneal transfusion of blood in dogs led first to a hyperplasia, and later to a true functioning of the bone marrow. They thought that the increase in hemoglobin due to the transfusion itself lasted only a few days.

Maas,[12] in 1881, injected small amounts of defibrinated blood into the peritoneal cavity of dogs and rabbits—after producing a secondary anemia. Blood counts taken five hours later showed an increase of from ½ to 2½ million cells per c.mm. The blood count gradually fell to normal. The increase in red blood cells varied directly with the amount injected.

---

5. Von Recklinghausen, F. V.: Zur Fettresorption, Virchows Arch. f. path. Anat. **26**:172, 1863.

6. Ponfick: Experimentelle Beiträge zur Lehre von der Transfusion, Virchows Arch. f. path. Anat. **62**:273 (Jan. 20) 1875; also Berl. klin. Wchnschr. **16**:589 (Sept. 29) 1879.

7. Bizzozero, G., and Golgi, C.: Della trasfusione di sangue nel peritoneo e della sua influenza sulla ricchezza globulare del sangue circolante, Arch. per. le sc. med., Torino **4**:67, 1880.

8. Poncet, quoted by Lesage: De l'hematocèle periuterine, These d'agregation, 1878.

9. Arloing and Tripier, quoted by Lesage: Recueil d. méd. vét. **7**:350 (June 15) 1900.

10. Obalinski, A.: Experimenteller Beitrag zur peritonealen Bluttransfusion, Przegl., lek. No. 9 i. 10 Polmsile; abstr. Jahresb. f. med. Wissensch., 1880, p. 314.

11. Foa, Pio, and Pellacani, Paolo: Ricerche sperimentali sulla trasfusione del sangue e sugli effetti delle scottature, Ann. med. **251**:478, 1880; abstr. Jahresb. d. ges. Med. **15**:312, 1880.

12. Maas, G.: Ueber intraperitoneale Bluttransfusion bei Thieren, Königsberg, Hartung, 1881.

In 1884, Hayem[13] reported an extensive and ingenious set of experiments, using rabbits and dogs. He obtained rapid and complete absorption of blood —whether defibrinated or not. He was never able to find any change in the morphologic structure of the red blood cells which were unabsorbed at the time necropsy was performed. He noticed that in case of autotransfusion, only a transitory anemia resulted. In cases in which an anemia was produced and an equivalent amount of blood injected, only a transitory anemia was apparent. On transfusing a normal animal, a plethora resulted. In order to prove definitely that the cells were absorbed as such, he hit on the idea of injecting rabbit's blood into the peritoneal cavity of a dog, with the intention of demonstrating the much smaller erythrocytes of the rabbit in the general circulation of the dog. However, he found that dog's blood contained hemolysins for the red blood cells of rabbits and he was able to show hemoglobin in the dog's serum. On trying the inverse experiment, on the other hand, he found the cells of the dog in the general circulation of the rabbit. He came to the conclusion that a peritoneal transfusion was equivalent to a very slow intravenous transfusion.

Marcus,[14] in a later publication, confirmed Hayem's results.

Ledderhose,[15] in 1885, demonstrated an increase in hemoglobin following the injection of blood into the peritoneal cavity of dogs.

William Hunter,[16] 1886-1887, working on rabbits, found that from 32 to 92 per cent. of the total amount of an animal's own blood could be injected intraperitoneally without ill effects. He got a slight rise in blood count with a subsequent fall on the second day, then a more permanent rise, reaching its maximum on the fifth or sixth day and persisting for about twenty-six days. He obtained similar results with defibrinated blood, but noted that the corpuscles were destroyed somewhat more rapidly than when using whole blood. He advised against this method as a therapeutic measure, chiefly because of the danger of peritonitis, and because only a relatively small amount of blood could be introduced at one time, and this, in turn, he thought, was rapidly destroyed.

In 1898, Southgate,[17] was able to transfuse an animal with the blood from another animal of the same species, and obtained an increase in red blood cells of 10, 11 and 4 per cent. at the end of the first, second and third hours, respectively. There was no hemoglobinuria. From further rather meager experimental data he drew the following conclusions:

1. Direct transfusion of arterial blood from one animal to the peritoneal cavity of another animal of the same species causes no perceptible injury to the animal receiving the blood.
2. Homogenous, nondefibrinated blood is quickly reabsorbed from the peritoneal cavity.
3. Homogenous blood reabsorbed from the abdominal cavity does not produce hemoglobinuria, but seems to be absorbed and to circulate as normal blood.
4. After hemorrhage, if there be sufficient compensation by transfusion into the peritoneal cavity, the general circulation changes very little or not at all.
5. Simple intraperitoneal transfusion of blood enriches the blood of the animal receiving it and the increase in corpuscular elements reaches its maximum in three hours.
6. Transfusion of foreign or heterogeneous blood into the abdominal cavity of rabbits produces hemoglobinuria and results in the death of the animal.

Vogel[18] opened the abdominal cavity of a rabbit, allowed a quantity of blood to flow into it from an artery and then closed the incision. At necropsy, seven days later, he found no blood or adhesions.

---

13. Hayem, M. G.: De la transfusion péritonéale, Compt. rend. **98**:748 (Jan.-June) 1884.

14. Marcus, S. H.: Die peritoneale Transfusion, Wien. med. Presse **25**:492, 1884.

15. Ledderhose: Beiträge zur Kenntniss des Verhaltens von Blutergüssen in serösen Höhlen unter besonderer Berücksichtigung der peritonealen Bluttransfusion, Strasbourg, 1885.

16. Hunter, William: Intraperitoneal Blood Transfusion and the Fate of the Absorbed Blood, J. Anat. & Physiol. **21**:138, 264, 450, 1886.

17. Southgate, F. H.: Ueber Blutresorption aus der Peritonealhöhle, Centralbl. f. Physiol. **8**:449, 1894; Blood Absorption from the Peritoneal Cavity, Med. Rec. **48**:221 (Aug. 17) 1895.

18. Vogel: Klinische und experimentelle Beiträge zur Frage der peritonealen Adhäsionen nach Laparatomien, Deutsch. Ztschr. f. Chir. **63**:363.

Lesage,[19] in 1900, reported his results in a series of experiments, using dogs and oxen. He found that, in dogs, absorption of blood following autotransfusion was complete in forty-eight hours, and that, at that time, the peritoneal cavity was absolutely normal in appearance. In a series of twenty-one animals, ranging in weight from 4 to 20 kilograms, transfused with from 75 to 200 c.c. of whole blood, and on whom the necropsy was made from forty-five minutes to forty-eight hours after the transfusion, there was complete absorption in three instances at the end of forty-eight hours. He found clots in the peritoneal cavity in nearly all his animals. In three other animals, receiving blood from another animal of the same species, absorption was complete in one instance at the end of forty-eight hours. In a later publication during the same year, he was able, by a very skilful method, to show the absorption of blood from the abdominal cavity. After an autotransfusion of 200 c.c. of blood obtained from the carotid and injected into the peritoneal cavity, he made a fistula of the thoracic duct. Forty-five minutes later the normally colorless, slightly opalescent lymph coming from the duct became rosy. The color gradually became more pronounced so that one hour after the operation it had a definite red tinge. Microscopic examination revealed large numbers of free red blood cells absolutely normal in appearance. No phagocytosis was demonstrable. However, at the necropsy, made forty-eight hours later, he found mononuclears gorged with red blood cells. He concluded that an hour after transfusion, red blood cells commence to pass freely without change into the thoracic duct. Then after the active diapedesis at the level of the peritoneum, the leukocytes come out and engulf the tardy red blood cells and go with them into the lymphatic circulation, the serosa returning to its normal aspect several days after the transfusion.

Skutsch,[20] in 1906, placed relatively large amounts of blood in the peritoneal cavity of rabbits and found complete absorption twenty-four hours later. He was unable to demonstrate any evidence of peritonitis, clots or adhesions.

In 1906, Buxton and Torrey,[21] in an extensive and thorough research, were able to show that after the injection of various foreign particles (lampblack, typhoid bacilli, hen's red blood cells, etc.) into the peritoneal cavity of guinea-pigs, there was an immediate rush of these particles to the lymphatics of the diaphragm. From there they passed along the anterior mediastinal lymph trunks, through the nodes, into the thoracic duct and finally into the blood stream. This took place very rapidly and the particles were practically in a free state. Phagocytosis was seen later, chiefly in the anterior mediastinal nodes.

In 1921, Zimmermann[22] was able to show that absorption of whole blood took place very rapidly from the abdominal cavity. Working on rabbits and guinea-pigs, he found that absorption was complete in forty-eight hours. There was no evidence of peritonitis at any time. He injected bird's blood into rabbits and guinea-pigs. He demonstrated the cells of the bird in the guinea-pig's circulation in five minutes. In the rabbits, nucleated cells were found from fifteen to thirty minutes after the injection. He found these cells in the thoracic duct and lymph nodes in large numbers.

CLINICAL EXPERIMENTS SHOWING ABSORPTION FROM PERITONEAL CAVITY

The intraperitoneal route for blood transfusion has been used by some men, but only in isolated cases.

Ponfick,[6] in 1875, encouraged by his results on animals, injected defibrinated blood into three patients with good results. He injected from 220 to 250 c.c. with only slight febrile reactions. He stated that it acted as a true trans-

19. Lesage, J.: Transfusion sanguine intraperitoneale, Recueil de med. Veterinaire **7**:350 (June 15) 1900; Sur la resorption du sang injecte dans la cavita peritoneale, Compt. rend. Soc. de Biol. **11**:553, 1900.

20. Skutsch: Die Entstehung der Hämatocoele, Arch. f. Gynäk. **77**:99, 1906.

21. Buxton, B. H., and Torrey, J. C.: Absorption from the Peritoneal Cavity, J. M. Research. **15**:5 (July) 1906.

22. Zimmermann, R.: Ueber die Indikationsstellung zur Retransfusion in die Bauchhöhle ergossenen Blutes, Ztschr. f. Geburtsh. u. Gynäk. **84**:334 (Nov.) 1921.

fusion and not as the introduction of nutrient material, because he found no hemoglobinuria. However, his conclusions are overdrawn because he did not make any blood counts before and after the transfusion.

In 1880, Golgi and Raggi[23] transfused an insane person, 38 years of age, with 310 c.c. of defibrinated blood. The hemoglobin rose from 35.8 to 44.1 per cent. in eighteen hours. Fourteen days later, the hemoglobin was 57.9 per cent. No bad effect was noted at any time.

During the same year, Mangiagalli[24] injected 200 c.c. of defibrinated blood into the peritoneal cavity of a woman suffering from hemorrhage following a placenta praevia, with very good results. However, she had another hemorrhage four days later and died.

Mosler,[25] in 1881, warned against the use of the intraperitoneal route because of the danger of peritonitis. He injected 40 c.c. of defibrinated blood in a case of idiopathic anemia without any good or bad results. Encouraged by this, he injected 130 c.c. of blood fourteen days later, and the patient died of acute peritonitis. He thought death was due to the too early repetition of the operation. However, at the necropsy there was no blood in the peritoneal cavity.

Scottini,[26] in the same year, transfused a farmer's wife, aged 45 years, with 270 gm. of defibrinated blood. There was only a transitory improvement. The patient died of anemia one month later.

Giovanni,[27] in 1881, injected 270 c.c. of defibrinated blood into a 9 year old girl, complaining of severe anemia. There was a steady improvement, which reached its climax on the fifteenth day.

Von Kaczorowski,[28] in 1881, reported five cases of transfusion into the abdominal cavity. He used defibrinated blood. No results are given.

Burresi,[29] in 1883, collected thirty-eight cases from the Italian literature and reported a case of his own. In his thirty-eight cases there was improvement in twenty-four, no effect in seven, and a bad effect in seven. He performed a transfusion on a patient with pernicious anemia using 250 gm. of defibrinated blood without any bad symptoms. The patient died six days later.

Liegl,[30] in 1884, reported a case of puerperal hemorrhage in which he injected 175 c.c. of defibrinated blood with good results.

MODE OF ABSORPTION OF BLOOD FROM THE PERITONEAL CAVITY

In 1862, von Recklinghausen[8] noticed a marked injection of the vessels on the pleural side of the diaphragm after the intraperitoneal injection of defibrinated blood. He found that resorption of carmin particles took place only through lymph channels. Urine specimens and serum showed no evidence of red. He covered the rabbit's diaphragm with milk and noticed a series of eddies where the fluid rapidly entered. After marking these places, he treated the diaphragm with silver nitrate and found corresponding black spots between the endothelial cells which he thought were the mouths of the

---

23. Golgi and Raggi: Trasfusione di sangue del peritoneo in un alienato oligocitemico, Gazz. med. ital. **7**:61 (Feb.) 1880; abstr. Jahresb. d. ges. Med. **15**:314, 1880.

24. Mangiagalli: Peritoneale Bluttransfusion, Zentralbl. f. Gynäk., No. 19, p. 463 (Sept. 11) 1880.

25. Mosler, F.: Ueber Gefahren der peritonealen Transfusion, Deutsch. Arch. f. klin. Med. **28**:476 (April 25) 1881.

26. Scottini, P.: Trasfusione di sangue nel peritoneo in una donna malata di grave anemia per anchilostomia, Ann. univ. di med. e chir. **255**:93, 1881; abstr. Jahresb. f. med. Wissensch. **16**:304, 1881.

27. Giovanni, A. de: Un caso di gravissima anemia felicemente mediante la trasfusione di sangue intraperitoneale, Raccolt. da Marzolo, Gazz. med. ital. **24**:39 (Nov.) 1881; abstr. Jahresb. f. d. ges. Med. **16**:240, 1881.

28. Von Kaczorowski: Fünf Fälle von Bluttransfusion in die Peritonealhöhle, Deutsch. med. Wchnschr. **6**:610, 1880.

29. Burresi, P.: Trasfusione sanguigna peritoneale in uno caso di anemia perniciosa, Sperimentale **52**:13, 1883.

30. Liegl: Ueber peritoneale Transfusion, Aerztl. Int.-Bl. **31**:33, 49, 1884.

lymph vessels—his so-called stomata. He concluded that "die tendinösen Theile des Zwerchfelles aus der Bauchhöhle nicht nur Flüssigkeiten resorbieren, welche mit Wasser nicht mischbar sind, sondern auch solche wässerige und ölige Flüssigkeiten, welche kleine Theile suspendirt enthalten."

Auspitz,[31] in 1871, confirmed these results.

Notkin,[32] in 1888, again repeated von Recklinghausen's experiments and further confirmed his results. He dissected out the thoracic duct in dogs and let the lymph flow out. He showed that free erythrocytes are found in the lymph after a period.

In 1893, Beck[33] treated the diaphragm of rabbits with silver nitrate and showed structures on the peritoneal surface of the central tendon which he thought were, without doubt, the openings of the lymph vessels into the peritoneal space. These communications formed short canals, lined with endothelium, which were continuous on one side with the endothelial lining of the peritoneal cavity, and on the other side, with the endothelium of the lymph vessels. After injecting bird's blood into the peritoneal cavity of dogs, and allowing the lymph to escape from the thoracic duct, he demonstrated red blood cells in the lymph in from one to two hours.

Starling and Tubby,[34] in 1894, injected indigo carmin and methylene blue in solution into the pleural and peritoneal cavities of animals, and observed the reappearance of pigment in the urine after ligation of the thoracic duct and after introducing cannulae and collecting the lymph before its entrance into the blood stream. They always found color in the urine before its appearance in the lymph stream, and concluded that there was a direct interchange between the fluid in the cavities and the blood in the vessels. They supported the blood vessel theory of absorption.

Hamburger,[35] in 1895, tied off the thoracic duct to see whether absorption would take place and found that resorption went on, but much more slowly. He concluded that the blood vessels played the more important rôle in resorption from the peritoneal cavity.

Cohnstein,[36] in 1895, from work on three dogs, concluded that isotonic solutions were taken up by the lymph vessels only; hypertonic and hypotonic solutions by the blood vessels.

Muscatello,[37] in 1895, in a very extensive and complete report of this subject, considered the diaphragm as the only point of absorption from the peritoneal cavity. From a large number of microscopic studies he concluded that there are no stomata in the diaphragm. He showed that these stomata are in reality artefacts, and that absorption took place by a process of active diapedesis of the injected particles. He suggested that the erythrocytes make their way between the endothelial cells for the most part in a free condition and only to a smaller degree, as the contents of phagocytes.

Robinson,[38] in 1897, injected a water solution of methylene blue into rabbits and dogs, and thought that he was able to make out stomata in the peritoneum which he held responsible for absorption.

---

31. Auspitz, E.: Ueber die Resorption ungelöster Stoffe bei Saügethieren, Stricker's med. Jahrb. **3**:284, 1871.

32. Notkin, J. A.: Vorläufige Mitteilung über Experimente zur Lehre vom Ascites, Wien. klin. Wchnschr. **1**:700 (Nov.) 1888.

33. Beck, A.: Ueber die Aufsaugung fein vertheilter Körper aus den serösen Höhlen, Wien. klin. Wchnschr. **6**: No. 46 (Nov. 16) 1893.

34. Starling, E. H., and Tubby, A. H.: On Absorption from and Secretion Into the Serous Cavities, J. Physiol. **16**:140 (Jan.-June) 1894.

35. Hamburger, H. J.: Ueber Resorption aus der peritonealhöhle, Centralbl. f. physiol. **9**:484, 1895.

36. Cohnstein, W.: Ueber Resorption aus der Peritonealhöhle, Centralbl. f. physiol. **9**:401, 1895.

37. Muscatello, G.: Ueber den Bau und das Aufsaugungsvermögen des Peritonäums, Virchows Arch. f. path. Anat. **142**:327 (Nov.) 1895.

38. Robinson, B.: Observations upon the Absorption of Fluids by the Peritoneum, Ann. Surg. **25**:332 (Jan.-June) 1897.

Meltzer,[39] in 1897, repeated the experiments of Starling and Tubby[34] and found that "colored fluid appeared invariably in lymph distinctly earlier than in urine." He advocated the lymphatic theory of absorption.

Starling,[40] in 1898, repeated his own experiments and obtained his original results.

During the same year Mendel[41] injected indigo carmin in dogs and collected lymph by a cannula in the thoracic duct and urine by a cannula in each ureter. In every case he found that color appeared in the urine long before it could be detected in the lymph of the thoracic duct. He favored the "blood vessel theory" of absorption from the peritoneal cavity.

In a series of papers (1901, 1904 and 1905) Sabin[42] proved conclusively that the lymphatic channels and ducts form a system which has no connection with the large serous cavities of the body. She regarded the lymphatics as modified veins, entirely independent of any openings into central thoracic spaces.

MacCallum,[43] in 1903, after careful microscopic studies of the diaphragm, concluded that the lymphatics were not in direct communication with the peritoneal cavity, but that in places, there was nothing between the two except the endothelial linings of the lymphatics on one side and the lining of the peritoneum on the other, with an exceedingly fine basement membrane between the two layers of cells. He thought that the lymph channels were enlarged at such points and that particles could be forced through by the pumping action of the diaphragm. His results closely confirmed those of Muscatello.[37]

Buxton and Torrey,[23] in 1906, after a large number of experiments, were unable to demonstrate a direct connection between the peritoneal cavity and the lymphatics of the diaphragm. They found, however, that after the intraperitoneal injection of suspensions, there was an "immediate rush of particles to the lymphatics of the diaphragm. From the diaphragm the particles were carried along the anterior mediastinal lymphatic trunks and through the lymph nodes, reaching the thoracic duct and blood current almost immediately after injection."

MATERIAL AND METHODS

With the exception of a few experiments in which the blood of pigeons was used, all our investigations were conducted on rabbits. Details of each series of experiments will be found in their respective order. We were careful to use healthy animals that had not been used for any previous work. A different rabbit was used for each experiment, so that no two transfusions were done on the same animal.

Blood was obtained in a few cases by cardiac puncture, in others, by the insertion of a cannula placed in a carotid, with the subsequent death of the animal.[44]

---

39. Meltzer, S. J.: On the Paths of Absorption from the Peritoneal Cavity, J. Physiol. **22**:198, 1897.

40. Starling, E. H.: On Absorption from Peritoneal Cavity, Proc. Physiol. Soc. Lond. **22**:24-26 (Jan.) 1898.

41. Mendel, L. B.: On Absorption from the Peritoneal Cavity, Am. J. Physiol. **2**:342, 1898.

42. Sabin, F. H.: On the Development of the Superficial Lymphatics in the Skin of the Pig, Am. J. Anat. **3**:183, 1904.

43. MacCallum, W. F.: On the Relation of the Lymphatics to the Peritoneal Cavity in the Diaphragm and the Mechanism of Absorption of Granular Materials from the Peritoneum, Anat. Anz. **23**: No. 6 (May) 1903; On the Mechanism of Absorption of Granular Materials from the Peritoneum, Bull. Johns Hopkins Hosp. **14**:105, 1903.

44. For aid in employing this procedure we are greatly indebted to Dr. R. A. Kriz.

However, we soon found that we were able to obtain blood easily and rapidly by venesection of one of the smaller vessels of the ear, after topical applications of xylol.

Our dosage for transfusion was almost uniformly 10 c.c. of citrated blood, independent of the weight of the recipient, and we were able to get this amount very readily by the foregoing procedure.

All the experiments were performed under aseptic conditions. At the end of each series, the animals were killed and every organ was carefully examined. In some instances, specimens for microscopic examination were taken.

All hemoglobin estimations were made with the von Fleischl-Miescher hemoglobinometer. Both hemoglobin values and erythrocyte counts were checked repeatedly and averages taken. In many cases, the urine and feces were examined for occult blood.

TABLE 1.—INTRAPERITONEAL TRANSFUSION OF WHOLE BLOOD

Exper. No.	Necropsy	Weight of Animal in Gm.	Quantity Transfused, C.c.	Amount Recovered at Necropsy, C.c.	Remarks
1	1½ hrs.	410	10	10	Clots over omentum, mesentery and in abdominal cavity. No injection of pleural surfaces
2	2 hrs.	920	10	7	No laking; few clots
3	2 hrs.	450	10	10	No absorption; clots. No injection of pleural surfaces
4	2½ hrs.	800	10	10	No absorption; clots
5	3 hrs.	870	10	6	Large clots present. No injection of pleural surface

PRESENTATION OF DATA

INTRAPERITONEAL TRANSFUSION WITH WHOLE BLOOD

It can be seen from our review of the literature that only defibrinated and whole blood have been used for experimental purposes. We did not attempt to use defibrinated blood because of the greater simplicity with which citrated blood can be obtained. However, in our preliminary experiments we did use whole blood intraperitoneally. All protocols and results obtained are shown in Table 1. In no case were we able to demonstrate absorption of the injected whole blood. In every instance, clots were present in the abdominal cavity at necropsy. The presence of clots in the peritoneal cavity with the subsequent formation of adhesions (Baisch [45]) makes this method inadvisable.

It must be remembered also that the formation of clots means the entanglement of a large proportion of the injected erythrocytes. Coagulation mechanically prevents their absorption, and the very object of their injection is defeated.

45. Baisch, K.: Klinische und experimentelle Untersuchungen über postoperativen Ileus, Hegars Beitr. z. Geburtsh. u. Gynäk. **9**:437, 1905.

Furthermore, it is a well known fact, that even in the intramuscular injections of whole blood, rapidity of procedure is vital, because the blood often clots in the syringe. In transfusing relatively large amounts of blood, this difficulty would be enhanced proportionately.

INTRAPERITONEAL TRANSFUSION WITH CITRATED BLOOD: IMPORTANCE OF FRESH SOLUTIONS AND IMMEDIATE INJECTION

We then attempted the use of citrated blood but, at the beginning, with very erratic results. After reviewing our technic, we found that we had overlooked two factors: We were using citrate solution that had not been freshly prepared, and we had allowed our citrated blood to stand three or four hours, and sometimes even over night, before giving it to the recipient. Table 2 shows the results we obtained and the

TABLE 2.—INTRAPERITONEAL TRANSFUSION OF CITRATED BLOOD—OBTAINED FROM THREE TO TWENTY-FOUR HOURS PRIOR TO OPERATION

Exper. No.	Necropsy	Weight of Animal in Gm.	Quantity Transfused, C.c.	Amount Recovered at Necropsy, C.c.	Remarks
6	30 min.	920	10	10	No laking. Congestion of abdominal side of diaphragm
7	1 hr.	850	10	12	No absorption
8	1 hr.	760	10	10	No absorption
9	2 hrs.	800	10	8	No absorption. No congestion
10	3 hrs.	800	10	13	No absorption. Peritoneum injected
11	3 hrs.	900	10	13	No absorption. No injection
12	3 hrs.	790	10	8	No absorption
13	4 hrs.	620	10	11	No absorption
14	4 hrs.	750	10	10	No absorption. No injection
15	4 hrs.	1,220	10	20	No absorption. Very dilute fluid
16	5 hrs.	820	10	12	No absorption. No injection
17	12 hrs.	900	40	40	No absorption. No injection; very viscous material

details of each experiment. It can be seen that, though clotting does not take place, there is practically no absorption from the peritoneal cavity, even after long periods of time (Experiment 17). In this series, there is apparent a tendency for an outflow of serum from the circulation into the peritoneal cavity (Experiment 15). This may be an attempt on the part of the body to equalize the difference in osmotic pressure probably present. A comparison with Table 1 shows that this phenomenon does not occur when whole blood is used. Perhaps, the citrate solution, which was not freshly prepared, may account for this difference.

Evidence Showing that the Cells Are Absorbed.—(*a*) Examination of Animals at Necropsy Following the Production of a Plethora: Using a uniform technic and preparing fresh solutions each time, we then transfused nineteen rabbits by the intraperitoneal route. Complete data and observations are given in Table 3. We wish to call particular

attention to the fact that in those animals showing apparently only little absorption, the fluid obtained at the necropsy did not resemble the blood that we had injected. It was more of the character of blood stained fluid. It can be noted that in every instance in which this occurred (Experiments 24, 25 and 31) the hemoglobin showed a definite rise varying from 8 to 14 per cent. This cannot be accounted for by a concentration of the blood volume and so we must assume that the absorption of erythrocytes is taking place rapidly.

At necropsy, the pleural surface of the diaphragm and the lymphatics leading from it were congested in every case. Smears were

TABLE 3.—INTRAPERITONEAL INJECTION OF FRESHLY CITRATED BLOOD OF NORMAL RABBITS

Exper. No.	Necropsy	Weight of Animal in Gm.	Quantity Transfused, C.c.	Amount Recovered at Necropsy, C.c.	Remarks
18	2 hrs.	720	10	0	Complete absorption; pleural surfaces of diaphragm injected
19	1 hr.	520	10	2	Absorption almost complete; pleural surface of diaphragm injected
20	2 hrs.	460	10	4	Absorption progressing
21	2 hrs.	770	10	..	Subcutaneous blood. No coagulation, no absorption
22	2 hrs.	790	10	0	Absorption complete. Injected lymph vessels
23	2 hrs.	1,120	10	4	Some hemorrhage at operation
24	2 hrs.	850	10	8	Blood fluid; Hb. rose from 57 to 68%. Injection of lymph vessels
25	2½ hrs.	800	10	11	Bloody fluid; Hb. rose from 52 to 60%
26	2½ hrs.	770	10	Few gtt. of blood-stained fluid	
27	2½ hrs.	460	10	0	Complete absorption
28	3 hrs.	800	10	0	Complete absorption
29	3 hrs.	700	10	4	Blood tinged fluid
30	3 hrs.	720	10	0	Complete absorption
31	3 hrs.	800	10	8	Bloody fluid. Hb. rose from 58 to 60% in 2 hours, then fell to 62%
32	4 hrs.	590	10	0	Complete absorption
33	4 hrs.	350	10	5	Small animal
34	4 hrs.	340	10	6	Small clot; smears normal
35	5 hrs.	370	10	0	Complete absorption, nearly ½ of its own blood volume
36	17 hrs.	1,010	15	0	Complete absorption

made of the peritoneal contents of all animals and in no instance did we find evidence of hemolysis. The cells appeared normal in size, shape and structure. There was no evidence of phagocytosis. A few polymorphonuclear and lymphocytic leukocytes were seen, but these have been shown to be normally present (Kanthack and Hardy [46]). Urine and feces examinations for occult blood and evidence of blood destruction were consistently negative.

According to Küttner,[47] the blood volume of a rabbit is approximately from one-nineteenth to one-twentieth of its body weight. On

46. Kanthack, A. A., and Hardy, W. B.: The Morphology and Distribution of the Wandering Cells of Mammalia, J. Physiol. **17**:81, 1894.

47. Küttner, H.: Experimentelle Untersuchungen zur Frage des künstlichen Blutersatzes, Beitr. z. klin. Chir. **40**:609 (Nov.) 1903.

this basis the animal used in Experiment 35 had a blood volume of about 19 c.c. Without producing any anemia, this rabbit received 10 c.c., or one-half of its own blood volume, intraperitoneally. Five hours later, the abdominal cavity showed no evidence of blood. Tests for blood in the urine and feces were negative. This shows clearly the remarkable absorptive capacity of the peritoneal cavity.

We concluded from this study that absorption in an average sized rabbit, when transfused intraperitoneally with approximately one fifth of its own blood volume, is complete in about four hours. There is, of course, a very apparent individual variability.

(*b*) Examination of Animals at Necropsy Following Autotransfusion: Table 4 shows the results obtained after autotransfusion of citrated blood. The amount transfused was taken in every case from the ear of the rabbit and injected immediately into its peritoneal cavity. Unfortunately, we made no blood studies on this group. It would appear that absorption under these conditions takes place more rapidly

TABLE 4.—INTRAPERITONEAL TRANSFUSION OF CITRATED BLOOD—AUTOTRANSFUSION

Exper. No.	Necropsy	Weight of Animal in Gm.	Quantity Transfused, C.c.	Amount Recovered at Necropsy, C.c.	Remarks
37	50 min.	870	10	5	Bloody fluid
38	90 min.	...	8	0	Complete absorption
39	3 hrs.	1,030	10	5	Injury at laparotomy with some bleeding
40	3 hrs.	1,020	10	0	Complete absorption
41	3 hrs.	800	10	0	Complete absorption
42	3 hrs.	870	10	0	Complete absorption

than in those animals that have not been bled. In these animals an anemia has been produced, and the transfusion is required. In the others, transfused without a preliminary depletion of the blood volume, a plethora is produced, absorption still takes place, but more slowly.

These observations, made at the necropsy table, where accurate data can be obtained, and results noted under direct vision, without the aid of instrumental assistance, show beyond doubt that absorption of citrated blood from the peritoneal cavity does occur. However, the question remains—Are the red blood cells absorbed as red blood cells or are they broken down and merely utilized as nutrient material?

Evidence Showing That the Cells are Absorbed Without Morphologic Changes.—(*a*) Recovery After Transfusion Following the Production of Severe Anemia: In order to determine this point more definitely, we performed the following experiments. Normal healthy rabbits were bled daily, small amounts at a time, until the hemoglobin fell to about 30 per cent. and the erythrocytes count to 3,500,000. Detailed data and mode of procedure are given in Table 5. After

TABLE 5.—Intraperitoneal Transfusion of Citrated Blood After Production of Severe Anemia

Exper. No.	Weight of Animal in Gm.	Original Blood Examination		Blood Picture Before Transfusion		Amount Injected in C.c.	Blood Picture Following Injection									
							1st Day		2d Day		3d Day		4th Day		5th Day	
		Hb %	R.B.C.	Hb. %	R.B.C.		Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.
43	1,000	53	5,580,000	30	3,000,000	18	33	3,360,000	35	3,170,000*	..	.....	..	.....	..	.....
44	1,140	55	5,400,000	28	2,950,000	22	29	3,060,000	..	.....	34	3,520,000	..	.....	35	3,900,000
45	1,050	54	5,870,000	31	3,200,000	31	37	3,860,000	..	.....	39	4,270,000	..	.....	41	4,470,000
46	1,150	54	5,500,000	36	3,800,000	25	42	4,500,000	41	4,250,000	..	.....	44	4,350,000	49	4,980,000
47	1,030	58	5,450,000	32	3,320,000	18	44	4,610,000	45	4,630,000	46	5,100,000	..	.....	56	5,900,000

* Animal died on 7th day.

TABLE 6.—Subcutaneous Injection of Citrated Blood Following Production of Anemia

Exper. No.	Weight of Animal in Gm.	Original Blood Examination		Blood Picture Before Transfusion		Amount Injected in C.c.	Blood Count Following Injection							
							1st Day		3d Day		5th Day		7th Day	
		Hb. %	R.B.C.	Hb. %	R.B.C.		Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.
48	1,050	58	5,250,000	29	3,100,000	15	30	3,170,000	33	3,980,000	32	3,630,000	32	3,630,000
49	950	53	5,420,000	30	3,340,000	20	31	3,380,000	31	3,880,000	25	3,920,000	25	3,490,000
50	1,000	56	5,300,000	34	3,300,000	20	32	3,400,000	34	3,500,000	34	3,340,000	35	3,400,000

TABLE 7.—Intraperitoneal Transfusion of Citrated Blood, After Production of Anemia, Showing Blood Changes

Exper No.	Weight of Animal in Gm.	Blood Before Experiment Hb. %	Blood Before Experiment R.B.C.	Blood Before Transfusion Hb. %	Blood Before Transfusion R.B.C.	Amount Injected, C.c.	Blood Picture Following Injection: 1 Hour Hb. %	1 Hour R.B.C.	3 Hours Hb. %	3 Hours R.B.C.	4 Hours Hb. %	4 Hours R.B.C.	2 Days Hb. %	2 Days R.B.C.	3 Days Hb. %	3 Days R.B.C.	6 Days Hb. %	6 Days R.B.C.	11 Days Hb. %	11 Days R.B.C.	Remarks
51	1,050	58	5,250,000	32	3,630,000	25	41	4,280,000	36	4,120,000	35	4,040,000	42	4,860,000	42	4,860,000	..	.....	..	.....	
52	1,040	55	5,400,000	41	4,050,000	22	48	5,760,000	47	5,840,000	43	4,700,000	47	5,150,000	54	5,960,000	54	5,490,000	56	5,500,000	Moderate anemia
53	980	56	5,300,000	38	4,000,000	20	47	5,400,000	45	5,500,000	42	5,100,000	46	5,390,000	51	5,670,000	53	5,540,000	52	5,600,000	Moderate anemia

TABLE 8.—Intraperitoneal Transfusion of Citrated Blood, in Normal Animals, Showing Blood Changes

Exper. No.	Weight of Animal in Gm.	Blood Before Injection Hb. %	Blood Before Injection R.B.C.	Amount Injected, C.c.	Blood Counts Following Injection: 1 Hour Hb %	1 Hour R.B.C.	3 Hours Hb. %	3 Hours R.B.C.	2 Days Hb. %	2 Days R.B.C.	3 Days Hb. %	3 Days R.B.C.	4 Days Hb. %	4 Days R.B.C.	5 Days Hb. %	5 Days R.B.C.	6 Days Hb. %	6 Days R.B.C.	9 Days Hb. %	9 Days R.B.C.
54	1,440	50	5,470,000	22	67	6,560,000	72	8,330,000	65	7,140,000	68	6,150,000	62	6,390,000	..	.....	60	5,730,000	60	5,800,000
55	1,150	55	5,250,000	21	67	6,300,000	67	6,850,000	67	6,540,000	68	6,700,000	69	6,800,000	..	.....	67	6,500,000	..	.....
56	1,350	51	5,400,000	16	60	6,480,000	63	6,370,000	57	5,730,000	60	5,700,000	..	.....	59	5,390,000	..	.....	..	.....

TABLE 9.—Showing Spontaneous Recovery Following Production of Severe Anemia

Exper. No.	Weight of Animal in Gm.	Original Blood Picture Hb. %	Original Blood Picture R.B.C.	Blood Picture Following Last Hemorrhage Hb. %	Blood Picture Following Last Hemorrhage R.B.C.	Blood Counts Following Injection: 1 Day Hb. %	1 Day R.B.C.	3 Days Hb. %	3 Days R.B.C.	5 Days Hb. %	5 Days R.B.C.	7 Days Hb. %	7 Days R.B.C.	8 Days Hb. %	8 Days R.B.C.	9 Days Hb. %	9 Days R.B.C.	14 Days Hb. %	14 Days R.B.C.
57	1.040	55	5,400,000	29	3,730,000	33	3,630,000	..	.....	38	4,440,000	41	4,050,000	..	.....	44	5,500,000	..	.....
58	950	54	5,390,000	30	3,930,000	30	3,040,000	36	4,180,000	45	4,420,000	..	.....	45	5,400,000	..	.....	44	5,140,000
59	980	55	5,370,000	28	3,560,000	30	3,360,000	..	.....	32	4,100,000	40	4,350,000	..	.....	43	4,480,000	..	.....

producing this severe anemia, varying amounts of citrated blood were injected into the abdominal cavity and blood examinations were made on the days indicated in the table. It will be seen that in three cases (Experiments 45, 46 and 47) there was a definite rise in hemoglobin estimations and blood counts, which persisted as long as the animals were under observation. In the three animals that responded, the hemoglobin increased from 31, 36 and 32 per cent. to 41, 49 and 56 per cent., respectively, in five days time. There appears to be a sharp rise in blood values following the transfusion. We know from our previous work that the transfused blood enters the circulation approximately in from three to four hours, and that the peritoneal cavity at that time is free of blood. Therefore, it is reasonable to assume that the rise in blood values is due to the fresh erythrocytes that enter the blood stream.

It may be noted that these animals did not react well. This may possibly be explained by the severe blood loss, amounting in some instances (Experiments 46 and 47) to 25 c.c., or almost one-half the total blood volume (Küttner [47]).

(*b*) Detailed Study of Blood Changes During the Absorption Period: From our postmortem studies we were led to suspect that changes occur during the period immediately following the introduction of the blood into the peritoneal cavity. We, therefore, produced a relatively mild anemia in three rabbits and made blood examinations at short intervals for four hours following the operation. Then the blood of these animals was examined over a period of days, as indicated in Table 7. The same procedure was performed also on three rabbits that were not bled, and in whom it was desired to produce a plethora (Table 8).

A comparison of the results is of interest. It can be seen that in the anemic animals there is a sharp rise at the end of the first hour. This initial rise is followed by a fall both in hemoglobin content and red blood cell count during the fourth hour. The gradual rise described by Hunter [16] and the subsequent fall on the second day, which is followed by a more permanent increase, reaching a maximum on the fifth or sixth day, are not confirmed by our experiences. On the second day the blood picture shows distinct improvement in every case, although it never reaches the peak attained at the end of the first hour. This is followed by a slow, gradual fall, yet at the end of nine days the hemoglobin and blood values are still distinctly improved over the initial counts.

In the control series (Table 8) in which a plethora is produced, the same characteristic initial rise at the end of the first hour can be observed. We were unable to get sufficient data to show the secondary fall which we believe does occur. The next day, the blood picture is

improved but again does not reach the values attained on the day of the operation. The tendency for the body to adjust itself and regain its normal blood volume by overcoming the plethora is well shown in the more rapid decline in the blood curve (Figs. 1 and 2).

Whether the initial rise in the blood curve in these animals is due merely to a concentration of blood volume or to an actual absorption of the transfused cells is, of course, debatable. The rapid disappearance

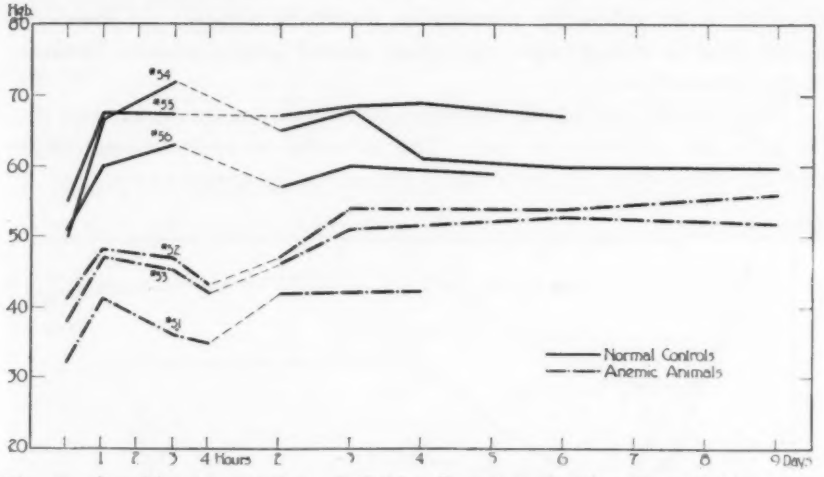


Fig. 1.—Graphic presentation of Tables 7 and 8 showing hemoglobin curve.

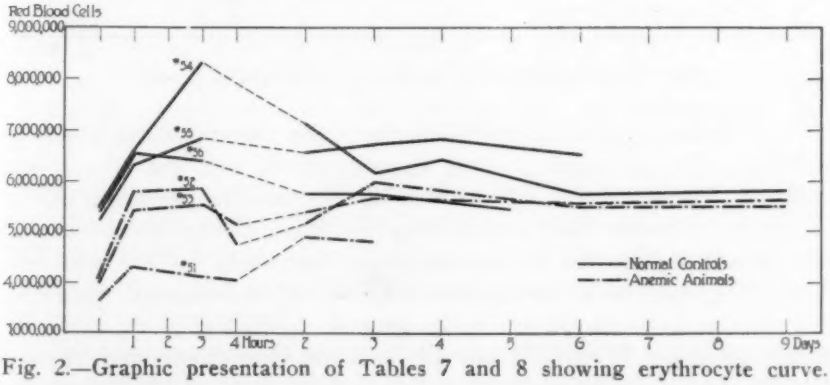


Fig. 2.—Graphic presentation of Tables 7 and 8 showing erythrocyte curve.

of the blood injected into the peritoneal cavity shown in Tables 3 and 4, and the fact that, in most cases, the residue still remaining at necropsy is steadily declining in amount are of significance. From our observations, gained at necropsies made on many animals, we incline to the opinion that the former factor plays a subordinate part.

Furthermore, a careful study of our material shows that there is a tendency for the red blood cell count to remain high and the drop in

hemoglobin is greater than the fall in erythrocytes. This ought not to be the case if a concentration of the blood volume is the dominant factor.

Tables 7 and 8 are presented in graphic form in Figures 1 and 2 in order to show the changes more clearly.

Another factor of importance is the behavior of the animals themselves. Immediately following the operation they act normally, and, throughout the entire experiment, they do not behave any differently from our normal controls. If toxic products are being produced and absorbed, some subjective phenomena should be present. If hemolysis of the cells is taking place, the urine should give a positive benzidin or guaiac reaction.

These results, we think, are sufficient to warrant the conclusion that the cells are absorbed as such. But in order to show beyond doubt that this does occur, we performed the following experiments.

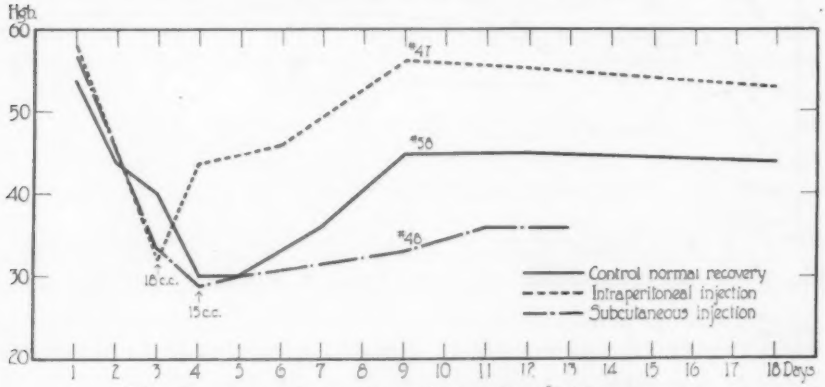


Fig. 3.—Comparison of methods; hemoglobin curve.

(*c*) Recovery of Pigeons' Cells from the General Circulation of Rabbits: Several pigeons were exsanguinated, and the blood was citrated. The citrated blood was then injected into the peritoneal cavity of rabbits. Smears were taken from the blood of the rabbits' ear at fifteen minute intervals for several hours, then daily for the next few days. We were able to demonstrate very clearly the elongated, nucleated red blood cells of the pigeon in the general circulation of the rabbit in fifteen minutes. These cells can still be found after twenty-four hours; but, in the specimens studied thus far, none were encountered later than thirty hours after the injection. These experiments show two things of supreme importance: First, the viability of the erythrocytes is demonstrated. Second, the red cells can pass from the peritoneal cavity into the general circulation without undergoing any morphologic changes.

Evidence Showing That the Cells Function.—At the present time we cannot present any positive evidence that the cells function after their

entrance into the blood stream. It appears reasonable, however, to expect that they meet the same fate that awaits red blood cells injected intravenously.

Boycott,[48] in 1910, working on rabbits, determined the total oxygen (hemoglobin) by Welcher's method and drew the following conclusions:

1. Blood transfused into the peritoneal cavity and subsequently absorbed into the circulation is destroyed more quickly than blood transfused by direct intravenous injection.
2. It is suggested that this difference is due to the red blood cells being rendered relatively more foreign by their passage through an extravascular position.
3. The mechanism of destruction is the same, except that phagocytosis of red cells in the lymphatic glands and spleen is much more prominent than with intravenous transfusion.

This work has never been confirmed. It may be noted that Boycott assumes that there is rapid destruction of cells introduced intravenously.

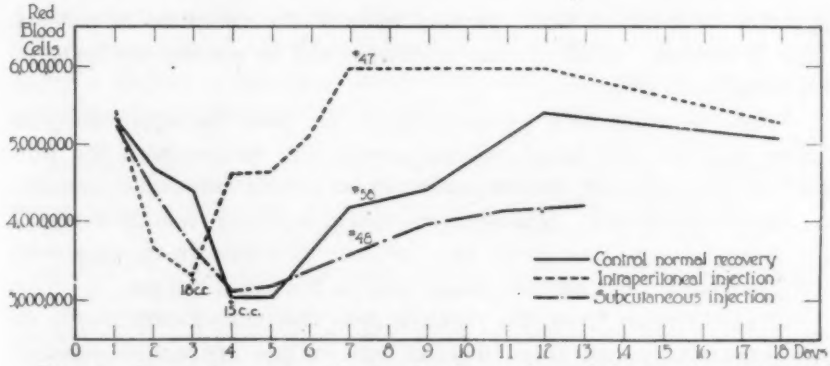


Fig. 4.—Comparison of methods showing value of intraperitoneal blood transfusion after production of severe anemia; erythrocyte curves.

Ashby [49] has recently proved "that the life of the transfused corpuscle is long." She states that "the beneficial results of transfusion are without doubt not due primarily to a stimulating effect on the bone marrow, but, it is reasonable to assume, to the functioning of the transfused blood corpuscles."

We may assume that our injected corpuscles do function because of the persistent, fairly permanent rise in blood values in anemic animals, following the transfusion, and because we have been unable to find any evidence, either from a laboratory or clinical standpoint, showing destruction of cells. In a subsequent paper we hope to present further data affording more conclusive proof that the erythrocytes function.

---

48. Boycott, A. E.: Peritoneal Blood Transfusion, J. Path. & Bacteriol. **14**: 605, 1909.
49. Ashby, W.: The Determination of the Length of life of Transfused Blood Corpuscles in Man, J. Exper. M. **29**:267 (March) 1919.

COMPARISON OF SUBCUTANEOUS AND INTRAPERITONEAL INJECTIONS OF CITRATED BLOOD

In order to compare the relative merits of the subcutaneous injection of citrated blood with the intraperitoneal transfusion, we produced an anemia in a series of rabbits, according to the method already described, and injected varying amounts of blood subcutaneously. Data and details of the experiment are given in Table 6. It can be seen that in no case was there any suggestion of a rise either in hemoglobin or in the erythrocyte counts. Even on the seventh day, there was no marked change in the blood picture. At the necropsy on these animals, a week later, there were present subcutaneous clots at the site of the injection.

A comparison with Table 9 reveals that the animals used as controls recovered from their anemia more rapidly than those receiving subcutaneous blood. The obvious conclusion is that the subcutaneous injection of citrated blood actually hinders the recuperative process. This is contrary to all of our teachings, and at present we have no explanation to offer.

While working with pigeon's blood, we took the opportunity to inject some of that blood subcutaneously into rabbits with the purpose of demonstrating the corpuscles in the circulation of the animal—if they are absorbed. Smears were taken at fifteen minute intervals for several hours, then every day for several days. In no case were we ever able to find pigeons' blood cells in the blood stream.

It would seem from this that the cells injected subcutaneously do not enter the general circulation, at least in any appreciable number. This confirms, in a striking way, the results obtained by Taylor.[50]

COMMENT

The Intraperitoneal Injection in General.—The intraperitoneal method of approach has been shown to be relatively safe by many men, Blackfan and Maxcy,[51] McLean and Lang,[52] Denzer and Anderson,[53] Gittings and Donnelly,[54] and others. At present the intraperitoneal injection of normal saline or glucose solution in dehydrated and

50. Taylor, R.: The Fate of Subcutaneously Injected Red Blood Cells, Am. J. Dis. Child. **20**:337 (Oct.) 1920.

51. Blackfan, K. D., and Maxcy, K. F.: The Intraperitoneal Injection of Saline Solution, Am. J. Dis. Child. **15**:19 (Jan.) 1918.

52. McLean, S., and Lang, C. A.: Fluid Injection in Dehydrated Infants, Am. J. Dis. Child. **19**:359 (May) 1920.

53. Denzer, B. S., and Anderson, A. F.: The Absorption of Fluids Injected Into the Peritoneal Cavity, Am. J. Dis. Child. **21**:565 (June) 1921.

54. Gittings, J. C., and Donnelly, J. D.: The Clinical Value of Intraperitoneal Injections of Salt Solution, Am. J. Dis. Child. **23**:124 (Feb.) 1922.

athreptic infants is a recognized therapeutic procedure (Marriott[55]). The injection of citrated blood offers no greater technical difficulties than does that of physiologic sodium chlorid solution.

During the course of our investigations we had occasion to use more than 100 rabbits. Intraperitoneal injection done without any special precautions was absolutely harmless. We never had any ill results. Evidence of adhesions or peritonitis was never noted.

The question as to whether the presence of blood in the peritoneal cavity is harmful or not is, of course, of supreme importance. Experimental data collected from all sources seems to indicate that there is no harm from blood in the abdominal cavity. It is true, however, that when whole blood was injected, numerous investigators found clots present when the animal was examined at necropsy.

Is the Presence of Blood in the Peritoneal Cavity Harmful?—Clinicians are very much divided as to the value of blood in the peritoneal cavity, resulting from an ectopic pregnancy or trauma. One group does not remove any blood at the time of operation; another school removes all the blood possible. The third and largest group takes a median course and removes only the clots present at the time of surgical interference.

Zweifel,[56] in 1903, in reporting twenty-one cases of ruptured ectopic pregnancies, concluded that it was dangerous to trust blood in the peritoneal cavity because blood made an excellent medium for bacterial growth.

Füth,[57] in 1905, reviewed the literature thoroughly and concluded that blood should always be removed.

Baisch,[48] in 1905, after a number of experiments on rabbits and from clinical observations, made the following statement: "Die wichtigste Rolle aber in der Aetiologie der Darmverwachsungen spielt, wie unsere Experimente unzweifelhaft und eindeutig ergeben, die Anwesenheit von Blut."

Werth,[58] is of the opinion that leaving a large amount of decomposable material in the peritoneal cavity was not proper from an aseptic standpoint, in the first place; and that even aseptic decomposition products of dying cells had poisonous properties.

Fehling,[59] Haim and Lederer[60] support these views.

Bröse,[61] in a series of papers, dating from 1891 to 1912, reported cases ending in death and in which at necropsy there was no evidence of sepsis or

55. Marriott, W. McKim: Some Phases of the Pathology of Nutrition in Infancy, Am. J. Dis. Child. **20**:461 (Dec.) 1920.

56. Zweifel, P.: Zur Behandlung der Hämatocelen, München. med. Wchnschr. **50**:1449 (Aug.) 1903.

57. Füth, H.: Ueber die Behandlung des intraperitonealen Blutergusses nach Tubenrupturen, Zentralbl. f. Gynäk., No. 43, p. 1315 (Oct. 28) 1905.

58. Werth: Die Extrauterinschwangerschaften, V. Winkels' Handb. d. Geburtsh. **2**:938, 1887.

59. Fehling, H.: Grundsätze und Erfahrungen in der Behandlung der Tubenschwangerschaft der frühen Monate, Arch. f. Gynäk. **92**:3 (Oct. 19) 1910.

60. Haim, E., and Lederer, Oskar: Erfahrungen über rupturierte Extrauterinschwangerschaft mit freiem Bluterguss in die Bauchhöhle, Monatschr. f. Geburtsh. u. Gynäk. **25**:1, 207, 1907.

61. Bröse, P.: Ueber die Giftigkeit des in die freie Bauchhöhle ergossenen Blutes, Ztschr. f. Gynäk., No. 35, Pt. 2, p. 1334, 1911; Ztschr. f. Geburtsh. u. Gynäk. **21**:211, 1891.

peritonitis, just blood in the cavity. In his opinion this pointed to a toxic absorption of decomposition products. He concluded that blood in the abdominal cavity should be considered as dead tissue of no use to the patient and at times very dangerous. He thought the fluid portion was especially toxic. In a later paper he suggested that the body may have developed a sort of anaphylaxis against its own proteins.

In 1911, Bumm[62] confirmed these results.

Löwenstein,[63] in 1911, reported two cases supporting Bröse's view as to the toxicity of the blood in the peritoneal cavity.

Els,[64] in 1913, advocated the complete removal of all blood from the peritoneal cavity. In thirty-one cases of ruptured ectopic pregnancies, he had one death. He thought the rise in temperature was due to absorption of blood and the rise in pulse to absorption of toxic products of decomposition. He found that the pulse and appearance of the patient improved after removal of blood.

On the other hand, men of equal ability urge the harmlessness and the value to be derived from leaving the blood alone. Veit,[65] Ekstein,[66] Frommel,[67] Flatau,[68] and others, leave everything in the abdominal cavity with good results. V. Franque[69] reports sixty-seven cases without any fatalities.

Most men, however, take the middle course, removing clots and leaving the unclotted blood to be reabsorbed. Olshausen, Gusserow,[70] Hannes,[71] Fritsch,[72] Hörrmann,[73] Fiedler,[74] Wagner,[75] Runge,[76] Zimmermann,[22] and others, remove only the large clots in the abdominal cavity.

---

62. Bumm, E.: Ueber die peritoneale Wundbehandlung. Was verträgt das Peritoneum, was nicht? Monatschr. **34**: (Aug.) 1911; Ztschr. f. Geburtsh. u. Gynäk. **70**:2, 312, 1911.

63. Löwenstein: Ueber die Giftigkeit des in die freie Bauchhöhle ergossenen Bluts, Med. Klin. **7**:1773, 1911.

64. Els, H.: Ueber die Giftigheit und Gerinnungsverzögerung des intraperitonealen Blutergusses nach Tubenruptur, Arch. f. Gynäk. **99**:167, 1913.

65. Veit, J.: Doederlein's Handb. d. Geburtsh. **2**: 1916. (Quoted by Lichtenstein.[82])

66. Ekstein, E.: Zur Kenntnis der Tubenschwangerschaft, Monatschr. f. Geburtsh. u. Gynäk. **5**:140, 1897.

67. Frommel: Zur Therapie und Anatomie der Tubenschwangerschaft, Deutsch. Arch. f. klin. Med. **45**: 1889.

68. Flatau: Muss bei der Operation geplatzter Extrauterinschwangerschaften des in die Peritonealhöhle ergossenen Blutes entfernt werden. München. med. Wchnschr., No. 2, p. 42 (Jan.) 1904.

69. Franque, V.: Ueber Blutungen in die freie Bauchhöhle bei Extrauterinschwangerschaft, Prag. med. Wchnschr., 1904, p. 295.

70. Gusserow, A.: Ueber hochgradigste Anämie Schwangerer, Arch. f. Gynäk. **2**: 1871.

71. Hannes: Die Notoperationen bei Extrauteringravidität, Prakt. Ergebn. der Geburtsh. **14**:3, 1909.

72. Fritsch: Die retrouterine Hämatocoele, Samml. klin. Vortr. **19**:449, 1875.

73. Hörrmann, A.: Zur Klinik und zur Therapie der ectopischen Schwangerschaft, Ann. d. Städt. allg. Krankh. z. München. **12**:246, 1907.

74. Fiedler: Beitrag zur Aetiologie, Diagnostik und Therapie der Tubargravidität, Deutsch. Ztschr. f. Chir. **95**:170 (Nov.) 1908.

75. Wagner, A.: Zur Behandlung der geplatzten Extrauteringravidität mit freier Blutung, Deutsch. med. Wchnschr. **38**:1457 (Aug.) 1912.

76. Runge: Beitrag zur Aetiologie, Symptomatologie und Therapie der Extrauteringravidität, Arch. f. Gynäk. **70**:690, 1903.

Clinical opinion is divided, but a review of the literature clearly shows that most men obtain excellent results by removing only the clots present in the abdominal cavity. The consensus of opinion appears to be that the fluid portion remaining is not only harmless, but it is also reabsorbed and is of distinct value (Zimmermann [22]).

However, the dangers of clotting with its subsequent results (Baisch [45]) must be borne in mind. It has been shown that clotting does not take place when a freshly citrated solution is used. The constant motion of the intestines resulting from peristaltic movements is probably an important factor in preventing the coagulation. We believe that the actual presence of fluid blood in the peritoneal cavity is without danger.

Clinical Observations as to the Value of Blood in the Abdominal Cavity.—Clinical experience shows the benefit of blood in the peritoneal cavity. It is a well known fact that women who have lost large quantities of blood following a ruptured tube as a result of an ectopic pregnancy recover astonishingly well. Similarly, in cases reported in the literature of ruptured liver or spleen, recovery apparently occurred very quickly from the anemia following the severe blood loss. On the other hand, patients who have suffered severe external hemorrhages from external injuries do not do so well or recover from their anemia so rapidly. In the one case, the hemorrhage is internal; in the other, external. In the former case, the blood can reenter the blood stream and function; while, in the latter case, there is a total loss of blood to the body.

Clinical experience shows that the blood is nontoxic. In 1914, Thies [77] suggested the retransfusion of blood found in the peritoneal cavity in cases of trauma. During the war Elmendorf,[78] Peiser,[79] Kreuter,[80] Ranft,[81] and others, utilized this method on injured soldiers with very good results. Lichtenstein [82] made use of this procedure in cases of ruptured ectopic pregnancies with good results. He reported

77. Thies, J.: Zur Behandlung der Extrauteringravidität, Ber. a. d. gynäk. Gesellsch. Zentralbl. f. Gynäk. **38**:1191 (Aug. 22) 1914.

78. Elmendorf: Ueber Wiederinfusion nach Punktion eines frischen Hämatothorax, München. med. Wchnschr., No. 1, 1917, p. 36, quoted by Lichtenstein: Arch. f. Gynäk. **109**:599, 1918.

79. Peiser, A.: Ueber Eigenbluttransfusion bei Milzzerreissung, Zentralbl. f. Chir. **44**:71 (Jan. 27) 1917.

80. Kreuter, E.: Ein weiterer Fall von Wiederinfusion einer intraabdominellen Massenblutung bei Leberruptur, Zentralbl. f. Chir. **44**:765 (Aug. 25) 1917; Zur Wiederinfusion abdomineller Blutungen, München. med. Wchnschr., No. 42, p. 1498 (Oct. 17) 1916.

81. Ranft, G.: Autotransfusion nach Milzruptur, Zentralbl. f. Chir., No. 47, p. 1019 (Nov. 24) 1917.

82. Lichtenstein, F.: Ohne Eigenbluttransfusion sollte keine wegen Tubenusur operierte Frau mehr an Verblutung sterben, Arch. f. Gynäk. **109**:599, 1918.

twenty-seven cases of retransfusion collected from the literature. This would seem to indicate that the possibility of the formation of toxic products in the blood is of comparatively slight consequence.

Evidence gathered from every available source points to the absorptive powers of the peritoneal cavity and to the value of blood in the abdominal cavity. We believe that this knowledge can be utilized clinically. The simplicity of the technic makes the intraperitoneal transfusion the method of choice in selected cases. It affords the only feasible method for the transfusion of large amounts of blood in children more than 18 months of age. The exposure of a vein in the elbow for direct intravenous transfusion is an operation that, for obvious reasons, frequently fails in the hands of the most skilful surgeon. The proposed method can be used by any one. It is rapid, simple and efficient.

SUMMARY

1. We have shown that freshly citrated blood injected into the peritoneal cavity of rabbits is absorbed because: (*a*) Necropsies at various intervals following the operation reveal that the quantity present in the abdominal cavity rapidly decreases in amount and that absorption of comparatively large amounts of blood is complete in three to four hours; (*b*) estimations of blood values demonstrate definite increases from the time the blood is transfused until the animal is killed.

2. We have shown that the erythrocytes enter the blood stream without undergoing any morphologic changes, because: (*a*) Smears of the fluid in the abdominal cavity taken at necropsy show no change in the size, shape or structure of the corpuscles and no evidence of hemolysis; (*b*) our experiments show a rise in hemoglobin and cellular elements following transfusions in normal and anemic animals which cannot be accounted for by a mere concentration of the blood; (*c*) nucleated red blood cells of pigeons when injected intraperitoneally into rabbits can be recovered from the general circulation in fifteen minutes, and can persist there for at least twenty-four hours.

3. We submit the following additional evidence that the erythrocytes function: (*a*) They enter the blood stream very rapidly and are therefore presumably in a functioning condition; (*b*) the increase in the blood values of our animals persisted for days; (*c*) after severe hemorrhage, the animals improved visibly following the transfusion; (*d*) no hemoglobinuria could be demonstrated at any time; (*e*) autotransfusion and retransfusion have been used successfully in man; (*f*) clinical experience with cases of internal hemorrhage as compared with external hemorrhage tends to show that the blood is reabsorbed in a functioning condition.

CONCLUSIONS

1. The intraperitoneal transfusion of citrated blood in rabbits is a safe procedure, simple to apply and efficient.

2. Absorption of blood from the peritoneal cavity of rabbits takes place very rapidly. A rabbit can apparently absorb approximately one fifth of its own blood volume in four hours.

3. The intraperitoneal transfusion in both anemic and normal animals causes a sharp, temporary rise in blood values during the absorptive period. This is followed later by a more permanent increase in the blood picture.

4. Studies at necropsy when considered with the blood counts would apparently indicate that the initial rise is due to an actual absorption of red blood cells from the peritoneal cavity, and not merely to a concentration of the blood volume.

5. Pigeon's blood injected subcutaneously in rabbits apparently does not enter the general circulation in demonstrable amount. The same blood injected intraperitoneally is absorbed very rapidly.

6. The intraperitoneal transfusion of freshly citrated blood acts as a true transfusion and not as the absorption of a nutrient material.

7. The intraperitoneal route for blood transfusions is proposed as a therapeutic method of merit.

CLINICAL APPLICATION

A. W., aged 2, was admitted to the hospital, Aug. 22, 1922, because of poor appetite, weakness and marked pallor since birth.

Physical examination was essentially negative.

Blood examination revealed hemoglobin, 38 per cent. (von Fleischl-Miescher) and a red cell count of 3,600,000. The blood Wassermann reaction was repeatedly negative.

On the tenth day, after the failure of medical treatment, he received 50 c.c. of citrated blood intraperitoneally. The hemoglobin and erythrocyte counts rose materially. Seven days later, he received 100 c.c. of citrated blood. The hemoglobin went up to 52.5 per cent., the erythrocyte count to 5,800,000. Six days later, another transfusion of 100 c.c. of blood was given intraperitoneally. The hemoglobin then was 63 per cent.; erythrocytes, 6,060,000.

The patient was discharged Oct. 10, 1922, showing marked clinical improvement. The hemoglobin was 70 per cent.; erythrocytes, 5,700,000.

CONGENITAL MALARIA

REPORT OF A CASE IN COLORADO *

R. P. FORBES, M.D.

DENVER

In a malarial community, cases of intra-uterine infection with the malarial parasite are rare. In fact, the possibility of such infection is denied by some authorities, although admitted by the majority. The occurrence of malaria in an infant, aged 7 weeks, would invariably be accepted as a postnatal infection in a malarial community. However, the anopheles mosquito has not been found in eastern Colorado, although Cockerell [1] has made a thorough search for the insect in this region. The possibility that an occasional anopheles could be brought to Denver on a train from Texas cannot be denied, but such a circumstance, especially in the case cited, seems very unlikely.

REPORT OF CASE

History.—Baby S., aged 7 weeks, was first seen, Nov. 14, 1921, on account of fever and restlessness. The patient was the second child, the first having died of pneumonia, one year previously. Both parents, born in Greece, asserted that their general health was good. There had been no miscarriages; the mother had had no illness or history of fever during this pregnancy, and at term, Sept. 28, 1921, was delivered of a 7 pound girl baby after a normal labor. The baby was said to have been blue at birth, but otherwise she was normal. It slept well and nursed well, gaining in weight for seven weeks.

Examination.—The patient was well developed, well nourished and of good color and weighed 9 pounds. The temperature was 100.8 F. Examination of the heart, lungs, throat and ears failed to account for the fever. For the following forty-eight hours, the baby seemed to feel better, but November 17 its temperature was 103.6 F. Physical examination was again negative. The urine was free from albumin, pus or bacteria. Another urinalysis and also a Pirquet test proved negative.

Course.—The patient had six febrile attacks at seventy-two hour intervals, before the periodicity was fully appreciated, and the parents were questioned as to a history of malaria. The mother then gave a history of an unusually severe quartan infection in Greece, seven years before, but asserted that she became free from all symptoms three months after coming to the United States in 1916.

December 5, the baby had its seventh febrile attack. The temperature was 103.2 F. It looked anemic; the hemoglobin was 40 per cent.; leukocytes, 5,850; erythrocytes, 3,440,000. The spleen was palpable 2 cm. below the costal margin. The patient was admitted to the Children's Hospital for further study and

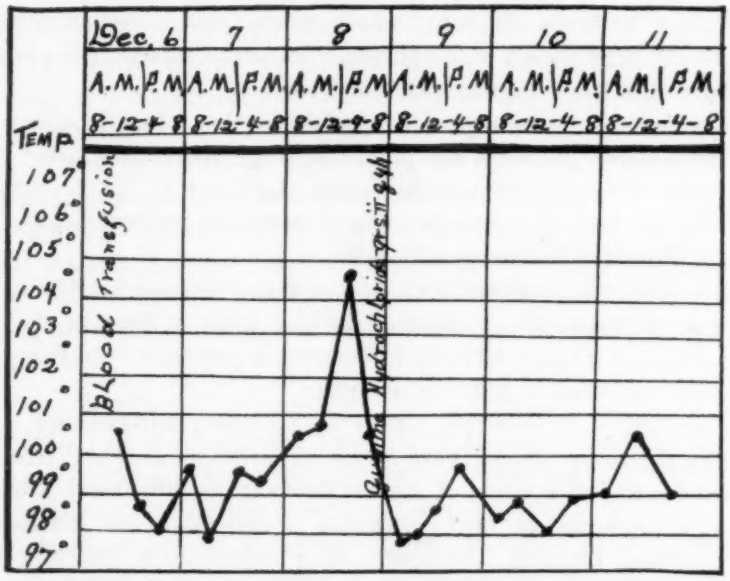
* Received for publication, Nov. 18, 1922.

* From the Department of Pediatrics, University of Colorado School of Medicine.

1. Cockerell, T. D. A.: The Mosquitoes of Colorado, J. Economic Entomol. **11**:195, 1918.

transfused with 110 c.c. of citrated blood from the father. Blood smears, taken at from twelve to twenty-four hour intervals, demonstrated large numbers of the malaria plasmodia in all stages of the asexual life cycle. On examination, the mother's blood at this time also showed quartan parasites. However, her spleen was not palpable.

Treatment.—On the morning of December 8, the parasites were full grown, the temperature rose to 104.6 F. Quinin hydrochlorid, 2 grains every four hours, was begun after this paroxysm and continued for four days; then it was given three times daily for four days, then three times on each of two days of each week for two months. Twenty days after quinin therapy was begun, the spleen could not be palpated. The baby had gained 26 ounces in fourteen days. At six months, the baby weighed 16 pounds, and had been free from any symptoms of malaria since treatment was begun.



Temperature curve before and after administration of quinin.

COMMENT

In 1910, Beekel [2] reported a case of malaria in early infancy, occurring in Cleveland, which is not in a malarial district, although the anopheles mosquito is found in Ohio. Beekel's case has many striking similarities to the case here reported. In his case the onset of malaria apparently occurred in the seventh week. The parents were of Hungarian origin, and both had suffered from malaria in Hungary, but had been free from symptoms for many years. Both had palpable spleens; but the organisms could not be found in their blood, although the patient's blood contained large numbers of quartan parasites until

2. Beekel, Fred.: Report of a Case of Malaria in Early Infancy, Cleveland M. J. **9**:879 (Nov.) 1910.

quinin was given. Beekel reviewed the literature to 1910, quoting twenty authorities, and found twelve cases of undoubted placental transmission. The accepted cases were those of Duschek,[3] Bohn,[4] Meara,[5] Crandall,[6] each one case, Hitte[7] two cases, and Economo[8] six cases. Economo found the parasites in the blood within forty-eight hours after birth, but some of his patients did not develop fever or symptoms. Economo concludes that the manifestations of the disease do not appear in the infant unless the mother had malaria during the latter part of pregnancy.

Since 1910, fifteen conclusive cases of congenital malaria have been reported. Bass[9] reports a case, occurring in midwinter in New York City, in a 4 weeks old baby, whose mother had a tertian infection during the fifth month of pregnancy. Postnatal infection is excluded by Bass on account of the season and location.

A summary of the reported cases shows that (1) all patients did not have symptoms when the plasmodia were found soon after birth, (Economo; Lamaire, Dumolard and Laffont[10]); (2) symptoms appeared at varying ages, the longest postnatal interval being seven weeks (Beekel;[2] Meara[5] and Bass[9]).

It is, therefore, reasonable to suppose that a new-born child can have a relatively latent type of malaria, and that some, at least, of the cases of malaria in infancy hitherto attributed to postnatal infection were, in reality, acquired in utero or at birth.

The method of infection cannot be explained satisfactorily. Bass believes that infection probably occurs at birth, since, if the fetus had been infected for a period of several weeks or months, there would be signs of cachexia at birth. Thayer, Pezopoulos and Cardamitis, Marchiafava, Bignami, and others deny intra-uterine infection from pathologic studies which failed to reveal the plasmodia in the fetal blood, in the cord, or on the fetal surface of the placenta, although the maternal blood contained parasites. However, the cases of Bohn, Pennato and Duschek, in which the stillborn fetus contained evidences of recent infection, show that intra-uterine infection actually may occur.

---

3. Duschek, quoted by Bohn: Jahrb. f. Kinderh. **6** (April) 1873.
4. Bohn: Das Wechselfieber und seine verschiedenen Formen im Kindesalter, Jahrb. f. Kinderh. **6**: (April) 1873.
5. Meara, F. S.: A Case of So-Called Congenital Malaria, Arch. Pediat. **26**:517, 1909.
6. Crandall: New York Polyclin. **1**:38, 1893.
7. Hitte, L.: Le Paludisme Congenital, Thésé de Montpellier, 1902.
8. Economo: Bull. de la Soc. d'obst. de Par. **10**:70, 1907.
9. Bass, Murray H.: Congenital Malaria, Arch. Pediat. **31**:251, 1914.
10. Lamaire, Dumolard and Laffont: A New Case of Congenital Malaria, Ann. de méd. et chir. enf. **14**:704, 1910.

Concetti [11] believes that a placental infarct is necessary to account for such infection. Thibault [12] examined the blood of 246 new-born infants whose mothers had active malaria, and found that only three of the babies had the parasites in their blood. Some abnormality of gestation or accident of delivery may therefore be safely presumed, since the parasites pass the placental filter so rarely. That active malaria is not necessary in the mother, as most authors have insisted, is shown by the cases of Beekel and by my own case. Kaufman [13] states that pregnancy is apt to bring into activity a latent malarial infection, but in Beekel's case and in my own case, no history of malarial symptoms during pregnancy was obtained from the mothers.

Besides the twenty-eight cases which I have considered conclusive, there have been reported eight cases in which the evidence is strongly in favor of intra-uterine infection. These cases have been reported by Jones; [14] Howard; [15] Josephson; [16] Moncorvo, [17] (three cases); Peters [18] and Mauca. [19] In spite of all the evidence in favor of true congenital malaria, some Italian authors are still skeptical. Sabella, [20] writing in 1911, quotes twenty-six authorities and concludes that congenital malaria does not exist. Mauca reported a probable case in a 27 day old infant, but since it came from a malarial district he doubts its congenital origin, as well as that of other cases reported.

CONCLUSIONS

1. The case here reported owes its chief interest to the fact that the anopheles mosquito can be excluded as the source of infection, and that intra-uterine infection, therefore, does occur.

2. Active malaria in the mother during the latter part of pregnancy is not essential for transmission of the disease to the fetus. In both Beekel's case and in my own the malaria was latent in the mother.

---

11. Concetti, L.: A Case of Congenital Malaria, La Propaganda Antimalarica Napoli **5**:14, 1912.

12. Thibault, H.: Congenital Malaria, J. Arkansas M. Soc. **12**:243, 1915.

13. Kaufman, B.: The Relation of Malaria to Pregnancy, New York M. J. **110**:1028 (Dec.) 1919.

14. Jones, D. W., and Moore, H. L., in discussion on Smith, M.: Malaria in Infants, South. M. J. **11**:213 (March) 1918.

15. Howard, W. A.: Letter to Editor, Pediatrics **8**:320, 1899.

16. Josephson, J. C.: Malaria in a Child of Three Weeks, Med. Rec. **59**: 635, 1901.

17. Moncorvo: Malaria in Children, Pediatria **8**:95, 143, 191, 239, 1899.

18. Peters, L.: Malarial Fever in Infancy, Probably Maternal in Origin. Bull. Johns Hopkins Hosp. **13**:139, 1902.

19. Mauca, M.: A Case of Malaria in the New-Born, of Probably Congenital Origin, Pediatria **22**:598, 1914.

20. Sabella, Pietro: On Congenital Malaria, Policlinico **18**:145, 1911.

SUMMARY OF THE TWENTY-EIGHT REPORTED CASES

Author	No. of Cases	Age Malaria Discovered in Infant	History of Malaria in Mother During Pregnancy	Plasmodia in Infant's Blood	Plasmodia in Mother's Blood	Remarks
Bohn[4]	1	Premature, dead	....	....	....	Necropsy evidence
Meara[5]	1	7 weeks	yes	yes	yes	
Duschek[3]	1	3 hours	....	....	....	Necropsy evidence
Crandall[6]	1	72 hours	....	yes		
Economo[8]	6	Within 48 hours	yes	yes		
Hitte[7]	2	At birth	....	yes	....	Blood from umbilical cord
Beckel[2]	1	7 weeks	no	yes	no	
Bass[9]	2	7½ weeks and immediately after birth	yes	yes	no yes	
Thibault[12]	4	2 hours	yes	yes		
		2 days	yes	yes	yes	
		5 days	yes	yes	yes	
		Dead at birth	yes	yes	yes	
Jones-Moore[14]	1	9 days	yes	yes		
Rabinoff[21]	1	Few hours	yes	yes		
Lamaire, Dumolard and Laffont[10]	1	Birth	yes	yes	yes	No symptoms till 40 days old
Tissier and Brumpt[22]	1	19 days	yes	yes	yes	
Leger[23]	1	Stillborn 7 months	yes	yes	yes	
Heiser[24]	1	5 days	yes	yes		
Bloom[25]	1	3 weeks	yes	yes	yes	
Caudra[26]	1	2 days	....	yes	yes	
Pennato[27]	1	Born dead	yes	....	....	Necropsy evidence

3. Malaria in the new-born may also be relatively latent but becomes active within a few weeks after birth.

4. Since malaria in pregnant mothers is common, but transplacental infection is quite rare, it is reasonable to presume that congenital malaria may depend on some abnormality of gestation or accident of delivery.

21. Rabinoff, Sophie: Some Experiences with Malaria Among Children in Palestine, Arch. Pediat. **37**:494 (Aug.) 1920.

22. Tissier and Brumpt: A Case of Congenital Malaria, Arch. méns. d'obst. et de gynéc. **3**:166, 1913.

23. Leger, M.: Congenital Paludism—a Case of Blood Infection of the Fetus by Plasmodium Vivax, Bull. Soc. de path. exot. **11**:841, 1918.

24. Heiser, V. G.: Malaria in the New-Born, Med. Rec. **84**:855, 1913.

25. Bloom, C. J.: Tertian Malaria in Two Infants Under Two Months of Age, Am. J. Dis. Child. **16**:391 (Nov.) 1918.

26. Caudra: Un cas de paludisme congenital, Arch. de méd. d. enf., 1920.

27. Pennato: Sulla malaria congenita, Riv. crit. di clin. med. **22**:85 (March) 1921.

THE EXCRETION OF FOREIGN PROTEIN IN HUMAN MILK*

HAROLD C. STUART, M.D.

BOSTON

In any series of infantile eczema cases studied by means of the cutaneous reactions to foreign proteins, the most perplexing problem which one encounters is the interpretation of reactions found positive to foods which, as such, have never entered the infant's diet. The frequent finding of a marked egg white reaction in early infancy, demonstrable on repeated applications, often in those exclusively breast fed, is the most notable example. Various explanations have been offered for such sensitizations. The most natural suggestion is that they are inherited, but, as Cooke and Vander Veer [1] have shown, the factor of inheritance seems limited to a tendency to develop sensitizations, a specific sensitization in the descendant rarely being traceable to the antecedents. A temporary transfer by the mother, such as is shown by animals, would not explain the delayed appearance of sensitization so often observed in infants, even if one assumed that the mother had an underlying sensitization which was in a refractory state when under observation. A quite different explanation suggests that the infants in question have become actively sensitized to proteins closely related to the ones giving positive tests, and that, therefore, the latter are evidences of "group" and not specific sensitization. I recently saw a young child who gave positive reactions to several of the nut proteins, although never having eaten nuts. It was later discovered, however, that cocoa also caused a reaction, and cocoa was being taken daily. Undoubtedly a "group" reaction explained the positive reactions to nuts. But in most infants there is no evidence of exposure to any related proteins. There are those also who believe that these skin reactions are not an evidence of sensitization at all, but merely an expression of a peculiar irritability of the skin. For such a theory to explain why some infants will repeatedly give egg white reactions and never respond to casein, while others will reverse this picture, it must presuppose a very specialized idiosyncracy on the part of the skin. This concept holds much in common with that of specific sensitization.

The theory given most credence of late is that these patients become sensitized by the direct transmission of unaltered protein through their

* Received for publication, Nov. 10, 1922.

* From the Department of Pediatrics, Harvard Medical School.

1. Cooke, R. A., and Vander Veer, A., Jr.: J. Immunol. **1**:3 (June) 1916.

mothers' milk. Lust,[2] Hayashi,[3] and Schloss and Worthen [4] have shown that under some circumstances an infant will absorb unaltered protein into its blood stream. Assuming that an adult may do the same thing under special conditions, it seems possible that such proteins might enter the breast milk. Clinically one occasionally sees an infant whose skin eruption improves when proteins to which it shows a positive reaction are removed from its mother's diet, but in my experience a striking relationship has been exceptional. In only one of the nine cases reported herewith did the addition or subtraction of these substances from the diet seem to produce corresponding changes in the condition of the skin. Because of such occasional cases, however, I sought to determine whether the presence of egg white protein is demonstrable, by guinea-pig experimentation, in the milk of mothers of infants that are sensitive to egg white, when they take rather large amounts of egg white. The breast milk collected from these mothers was used in an attempt both to sensitize and to shock guinea-pigs. The intravenous and the uterine strip methods were originally employed for the shock injection, it being felt that the latter would be the more satisfactory in providing graphic tracings of results, but the former would be more satisfactory in offering suitable confirmatory evidence, at the same time allowing the use of male pigs.

Shortly after undertaking this work, Shannon [5] published some experiments dealing with the same type of case, but using the intrathecal method of Besredka for his second or shock injection. From his results he concluded that egg protein does appear in the breast milk of mothers under these circumstances. This conclusion was based on tests made on milk collected from three mothers, whose diets contained from one to six eggs daily, the milk being collected from four to twelve hours after the ingestion of the last eggs. Seven guinea-pigs were first sensitized to egg, and after an interval of from twelve to fourteen days they were given an intrathecal injection of one of the breast milk specimens, followed after some time by an intraperitoneal injection of 1 c.c. All these guinea-pigs had marked reactions, and died within twenty-four hours, none, however, within the first few hours. One guinea-pig was sensitized with milk collected about four hours after the mother had eaten two eggs, and it was given a shock injection of egg white intrathecally, the reaction being mild, with complete recovery. As controls one guinea-pig was shocked and one was sensitized with breast milk from

2. Lust: Jahrb. f. Kinderh. **77**:244, 283, 1913.

3. Hayashi, J.: Monatschr. f. Kinderh. **12**:749, 1914.

4. Schloss, O. M., and Worthen, T. W.: Undigested Protein, Am. J. Dis. Child. **11**:342 (April) 1916.

5. Shannon, W. R.: Demonstration of Food Proteins in Human Breast Milk by Anaphylactic Experiments on Guinea-Pigs, Their Probable Relationship to Certain Diseases of the Nursing Infant, Am. J. Dis. Child. **22**:223 (Sept.) 1921.

one of the mothers after she had been on an egg free diet for two weeks. Six normal guinea-pigs were also given intrathecal injections of the same samples of breast milk as those used in the test guinea-pigs, and no reactions were obtained. Briefly, eight tests guinea-pigs all showed reactions, while eight control guinea-pigs showed no reactions. A few drops of milk from the mother that took only one egg a day (the interval after the taking of this egg not being specified) contained sufficient egg protein to determine a positive reaction. Again, in a later article, Shannon [6] mentions having also demonstrated the presence of veal protein in the milk of mothers whose infants gave a positive veal cutaneous reaction; but none of the details of this work are given.

Owing to the rather small series presented by Shannon, and because of certain considerations relating to his method which will be discussed later, I determined to continue my work and, if possible, to confirm the findings already published, using methods which I believe to be more suitable for this type of investigation. It seemed to me that if egg protein is demonstrable in breast milk when injected intrathecally, it should also be demonstrable by the intravenous route, or by the uterine strip method. I was particularly anxious to obtain graphic tracings which would eliminate the personal element in the interpretation of mild anaphylactic responses.

REPORT OF CASES

CASE 1.—P. Z., aged 3 months, had had eczema since the early weeks of life. The child was breast fed for the first two months, but the eczema had been worse since the addition of one bottle of milk at that time. Skin reactions were positive to both egg white and cow's milk. Both these substances were removed from the mother's diet, after collecting milk for tests, and the infant was given only breast milk. Minute doses of egg white and cow's milk were started by mouth. The skin became clear in three weeks, and the infant was weaned and given Dryco at the end of the course of treatment, without recurrence.

CASE 2.—M. G., aged 2 months, had had eczema since the second week of life. The infant had been partly bottle fed and partly breast fed, but gave no reaction to cow's milk protein. Egg white caused a marked cutaneous reaction. Since the mother had very little milk, it was used in experiments directly, without first giving the mother an egg free diet. The baby was completely weaned soon afterward. This was followed by disappearance of the eczema. The eczema returned two months later during the course of oral desensitization to egg white.

CASE 3.—E. B., aged 10 months, had eczema of four months' duration. It was a breast fed baby. The reaction to egg white was positive. The mother was given an egg free diet for two weeks. No change in the condition of the infant resulted.

CASE 4.—G. C., aged 6 months, was entirely breast fed, but had had eczema since 6 weeks of age. Cutaneous reactions were markedly positive to egg white, lactalbumin, casein, cow's milk and goat's milk. Egg was eliminated, but milk was only reduced in amount, as it was felt to be important to keep the mother's supply of milk up to the infant's requirements. No striking change occurred in the skin manifestations.

---

6. Shannon, W. R.: Minnesota Med. **5**:137 (March) 1922.

CASE 5.—M. C., aged 8 months, was entirely breast fed, but had had eczema since the fourth month. Cutaneous reactions were markedly positive to egg white, and lactalbumin; faintly positive to casein and goat's milk. Milk was collected directly without observing the effect of limiting the mother's diet.

CASE 6.—O. P., aged 4 months, had had eczema since the early weeks of life. The egg white reaction was the only one that was positive. The mother was put on an egg free diet for ten days. There was some improvement in the eczema, but it was still quite active at the end of the period, when milk was collected for tests.

CASE 7.—This was a patient of Dr. F. S. Churchill of Milton, Mass., to whom I am indebted for the samples of milk and the information regarding this case. The child was a 6 months' old infant that had showed skin reactions markedly positive to egg white and cow's milk. The eruption cleared rapidly after removal of these foods from the mother's diet. It returned on several occasions on the day following ingestion of egg by the mother.

CASE 8.—M. M., aged 8 months, had had eczema of four months' duration. Egg white was the only protein causing a positive reaction. The baby was completely weaned shortly after testing the milk, but the eczema did not clear up for several months on an egg free diet.

CASE 9.—J. C., aged 4 months, had had eczema since 5 weeks of age. The child was very much overweight for its age. It showed cutaneous reaction only to egg white. Milk for tests was collected first; the mother was then put on an egg free diet. Very gradual improvement occurred in the skin eruption. (The child was lost sight of before the eczema had completely disappeared.)

PROTOCOLS OF EXPERIMENTS

EXPERIMENT 1.—Egg sensitive guinea-pigs were tested with breast milk intravenously. Guinea-pigs were sensitized intraperitoneally with 0.1 c.c. of a one-tenth to one-fiftieth dilution of filtered egg white. The egg white was cut up before making the dilutions, but the ultimate filtering, particularly in the more concentrated dilutions, usually removed some of the egg white. Therefore, the dilution as given in the tables of all the experiments represents a slightly lower concentration than that actually given. The test injection was given at an interval of from three to sixteen weeks after the sensitizing injection, control guinea-pigs being shown to be sensitive at these intervals, and after these doses. Many of the guinea-pigs were given an injection of egg white on the day following the test injection, and all guinea-pigs thus treated died directly in typical anaphylactic shock.

Breast milk from the mothers of five of the nine infants was used in this experiment. Believing that egg protein would be present in the breast milk, in very minute traces, if at all, I attempted to make this concentration as great as possible by collecting the milk at definite intervals after the ingestion of large amounts of egg white. Different intervals were tried, owing to lack of knowledge regarding the time required for such protein to enter the milk. Separate specimens covering various intervals up to nine hours were collected, in some guinea-pigs being used separately, in others several such specimens being mixed. In addition, all but two of the mothers were on a diet containing from two to four cooked eggs a day for some time prior to the tests. These two mothers had been on an egg free diet for from one to two weeks, and a specimen of milk taken before the ingestion of the eggs served as a control in one of them. Milk when collected was skimmed but not heated. Doses ranging from 0.6 to 2 c.c. were injected into the jugular vein, the usual dose being from 1 to 1.5 c.c.

Eleven of the thirteen test guinea-pigs showed absolutely no reaction. The remaining two looked sick for the first one half to two hours, shivering and

occasionally showing gross rigor, but these were in no way suggestive of the involuntary twitchings and the bucking movements of true anaphylaxis. No guinea-pigs died as a result of the injection; none showed convulsive movements, and no symptoms were detected which were not detected in control guinea-pigs. Eight normal control guinea-pigs were given from 1 to 2 c.c. of similar samples of breast milk, and two of these shivered and looked sick after injection. Normal guinea-pigs given larger amounts of milk intravenously showed these toxic symptoms so regularly that 2 c.c. was set as the upper limit. The mild reactions to the smaller injections shown by two test and two control guinea-pigs were likewise considered toxic.

Four egg sensitive guinea-pigs were given breast milk, to which small amounts of egg white were added. Three of these guinea-pigs died with typical convulsions within five minutes, while the fourth guinea-pig had severe convulsions but recovered. In Guinea-Pig 191 less than 0.0002 c.c. of egg white added to breast milk caused severe convulsions.

Experiment 2.—Guinea-pigs were injected intraperitoneally or subcutaneously with various samples of breast milk collected from mothers of eight different infants suffering with eczema, from 2 to 7 c.c. being used intraperitoneally, and from 6 to 15 c.c. subcutaneously. In a few cases this milk was heated to 65 C. for twenty minutes before injection, because it was collected outside under unsterile conditions, but usually fresh milk was used lest even this amount of heating might alter the sensitizing power of the protein. The milk was collected at intervals up to twenty hours after the mothers had eaten both raw and cooked eggs. The interval allowed for sensitization ranged from fourteen (in one guinea-pig) to thirty-three days, the second injection being from 0.2 to 1.5 c.c. of a 1:5 or 1:10 dilution of egg white intravenously. Of the twenty-one test guinea-pigs in this series, sixteen showed absolutely no reaction, while the other five showed only the restlessness and shivering noted in some of the seven controls. Five of these were subsequently shown to have been sensitized to breast milk, while the others were not tested in this manner.

In the case of one control guinea-pig egg white was added to the sensitizing injection of breast milk, and the animal died in typical shock when reinjected with egg white.

Experiment 3.—Guinea-pigs were sensitized to egg white intraperitoneally as in Experiment 1. After an interval of three or more weeks (in one case only eleven days) the animals were killed and the uteri set up in apparatus described by Dale.[7]

Virgin guinea-pigs were used, weighing, when killed, from 225 to 375 gm. It was found that breast milk in concentrations of 1:50 or stronger would regularly cause contraction of the uterine strip in control guinea-pigs, but a concentration of 1:100 did not prove toxic (Guinea-Pigs 35, 100, 128, 25, 22, 39). In the tests, therefore, sufficient milk was added to the Ringer's solution to make a final dilution of 1:100 or 1:150. Milk from six mothers was used, the milk having the same relation to the ingestion of eggs as noted in the previous experiments. The milk was used without heating.

The muscle strip was first allowed to become quiet and the kymograph was started to get a quiet base line. Test breast milk, control breast milk and egg white dilutions were then added in various sequences, the reaction to the egg white proving that the guinea-pigs were sensitized. No contraction was produced in any animal by concentrations of test breast milk which did not produce reactions in controls. The curves obtained in two of these guinea-pigs are given. This experiment, however, was not found to be so satisfactory as the reverse procedure described under Experiment 4, because of the toxic action of breast milk on the uterus, when present in high concentration.

7. Dale, H. H.: J. Pharmacol. & Exper. Therap. **4**:167, 1912.

EXPERIMENT 4. — Guinea-pigs were sensitized with the breast milk either subcutaneously or intraperitoneally, and, after an interval of from eighteen to thirty-three days, were killed and the uteri set up in the Dale apparatus. This experiment was found to be the most satisfactory of all because it permitted the use of the test material for sensitizing, which is known to require a smaller dose than shocking; and further egg white in concentrations of 1:250 in Ringer's solution caused no irritation of normal muscle, whereas 1:50,000 would cause marked contractions in sensitized uteri. Tracings were taken of eleven test

Fig. 1 (Experiment 3, Case 8, Guinea-Pig 171, weight, 250 gm.).—Tracing made eleven days after the guinea-pig had been given 0.1 c.c. of a 1:50 dilution of egg white intraperitoneally: *A*, results following application of breast milk, collected three hours after the mothers had eaten the last two eggs (cooked) in the diet, to which had been added sufficient Ringer's solution to make a 1:150 concentration; *C*, results following the application of breast milk in the same concentration, collected six hours after the ingestion of eggs; *E*, results following the application of breast milk collected nine hours after the ingestion of eggs; *F*, effect of application of an egg white dilution added in a concentration of 1:500. The resulting contraction was immediate and complete. In this illustration and in Figures 2 and 4, time markings are in minutes, and breaks in the line indicate changes of Ringer's solution.

guinea-pigs (i. e., guinea-pigs sensitized with test breast milk), and not one of these showed any reaction to egg white, but all gave typical anaphylactic curves when breast milk was added. Normal guinea-pigs and guinea-pigs sensitized to egg white were both used as controls. Two of the tracings of the test guinea-pigs are given.

An analysis of these protocols and the accompanying tables reveals not the slightest suggestion of anaphylactic reactions in any of the

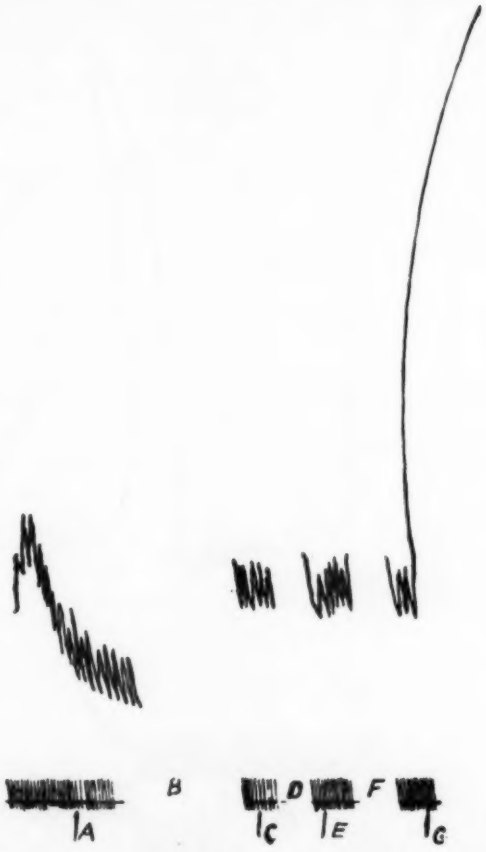


Fig. 2 (Experiment 3, Case 8, Guinea-Pig 126, weight, 300 gm.).—Tracings made thirty-five days after guinea-pig had been sensitized with 0.1 c.c. of a 1:10 dilution of egg white intraperitoneally: *A*, results of application of breast milk collected three hours after the ingestion of eggs; *C*, results following the application of breast milk collected six hours after the ingestion of eggs; *E*, results following the application of breast milk collected nine hours after the ingestion of eggs; *G*, results following the application of egg white in concentration of 1:150, causing immediate complete contraction.

test guinea-pigs. We had looked more hopefully to Experiments 2 and 4, those in which the breast milk had been used to sensitize, because much larger amounts of milk could be used for this purpose, and it is known that smaller amounts are required to sensitize than to shock.

These experiments did prove to be the most satisfactory because breast milk occasionally produced mild toxic symptoms when introduced intravenously and when added to the uterine strip, both in tests and in controls; whereas egg white proved to be nontoxic in very large doses. But the tables show that as much as 15 c.c. of breast milk collected after the ingestion of large quantities of egg failed to sensitize. It occurred to me that the great preponderance of breast milk protein in

Fig. 3 (Experiment 4, Case 8, Guinea-Pig 199, weight, 270 gm.).—Tracings taken three weeks after guinea-pig had been sensitized with 5 c.c. of milk collected after six hours, subcutaneously: *A*, results after application of egg white in concentration of 1:500; *B*, results following the application of mixed sample of breast milk in concentration of 1:200. Contraction was complete. The time tracings are in minutes.

the test material might in some way inhibit the action of the egg protein, so a number of control guinea-pigs were injected with breast milk containing a very small amount of added egg white, as shown in the tables. These injections were capable of shocking sensitive guinea-pigs and

Fig. 4 (Experiment 4, Case 8, Guinea-Pig 200, weight, 225 gm.).—Tracings made eighteen days after guinea-pig had been sensitized with 5 c.c. of mixed nursings from a mother taking four cooked eggs a day: *B*, results following the application of Ringer's solution to which had been added egg white in a dilution of 1:1,000; *C*, results following the application of a mixed sample of breast milk added in a concentration of 1:200. Immediate complete contraction resulted.

TABLE 1 (EXPERIMENT 1).—GUINEA-PIGS SENSITIZED WITH EGG WHITE INTRAPERITONEALLY: SUBSEQUENT INJECTION WITH SKIMMED FRESH BREAST MILK INTRAVENOUSLY

Case	Guinea-Pig	Amount Egg White Dilution, C.c.	Dilution Egg White	Interval Between Injections, Days	Amount Second Injection Breast Milk, C.c.	Description of Milk Used, i. e., Relation to Egg in Diet Form in Which Eggs Taken	Reaction	Subsequent Injections or Necropsy Findings
1	12	0.4	1:40	57	1.5	Mother eating 2 eggs twice daily (cooked). Mixed of 3 nursings	None	
2	2	0.4	1:40	110	0.6	Four raw whites given in milk. Milk collected 3, 6 and 9 hours after, mixed in equal parts	None	Necropsy negative
3	10	0.4	1:40	110	1.5	Four raw whites given in milk. Milk collected 3, 6 and 9 hours after, mixed in equal parts	Shivered and showed gross rigors first hour. Looked sick rest of afternoon. Normal next day	24 hours later given 0.1 c.c. of 1:5 egg white intravenously. Died in 3 min. in convulsions. Necropsy negative
4	16	0.5	1:25	63	1.5	Four raw egg whites given in milk. Specimen collected 2 hours later	None	24 hours later given 0.1 c.c. of 1:5 egg white dilution intravenously. Guinea-pig died in convulsions in a few minutes
4	30	0.3	1:10	27	1.5	Four raw egg whites. Milk collected 5 and 8 hours after (mixed)	None	24 hours later given 0.5 c.c. of 1:5 egg white dilution intravenously. Died in 10 minutes with convulsions
4 Control	28	0.3	1:10	28	1.5	On egg-free diet 2 weeks	None	24 hours later given 0.1 c.c. of 1:5 egg white. Died in 10 minutes with convulsions
8	121	0.1	1:10	34	1.5	Eating 4 cooked eggs daily. Milk of 3 nursings mixed	None	Following day given 0.3 c.c. of 1:10 egg white intravenously. Died with convulsions in 3 minutes
8	127	0.1	1:10	34	1.5	Eating 4 cooked eggs daily. Milk collected 3 hours after last eggs	Shivered violently first half hour. Otherwise normal	Killed in 2 minutes following day by injection of 0.3 c.c. of 1:10 egg white
8 Control	195a*	...	....	...	...	Same as Guinea-Pig 127	Scratched nose violently several times. Shivered first hour	
9	188	0.1	1:10	66	1.0	Taking 4 cooked eggs daily. Milk collected 2 (also 6) hours after last eggs	None	24 hours later given 0.1 c.c. of 1:5 egg white intravenously. Died in 3 minutes in convulsions

9	189	0.1	1:10	66	1.25			
9	185	0.1	1:10	66	1.5			
9	186	0.1	1:10	66	1.0			
9	187	0.1	1:10	66	1.0			
9	212	0.1	1:10	48	1.5			
Control	231*	...	....	...	1.5	Taking 4 cooked eggs daily. Milk collected 2 (also 6) hours after last eggs	None	
Control	237*	...	....	...	1.5			
Control	240*	...	....	...	1.5			
Control	241*	...	....	...	1.0			
Control	164*	...	....	...	1.5			
Control	166*	...	....	...	1.5			
Control	167*	...	....	...	2.0	Taking 4 cooked eggs daily. Milk collected 2 (also 6) hours after last eggs	Shivered and hair puffed out 15 minutes	
Control	118	0.1	1:10	58	1.5	Mother of normal infant, eating eggs twice daily	Shivered few minutes and looked sick 2 hours. Then normal	Following day given 0.5 c.c. of 1:10 egg white intravenously. Died in convulsions in 3 minutes
Control	150	0.1	1:10	20	2.0	Mother of normal infant, eating eggs twice daily	None	Injected like Guinea-Pig 118, and died in typical convulsions in 2 minutes
Control	184	0.1	1:10	66	1.0	Milk of Case 10 containing 0.1 c.c. of 1:10 egg white	Died in typical convulsions in 5 minutes	
Control	204	0.1	1:50	66	1.0	Milk of Case 10 containing 0.1 c.c. of 1:10 egg white	Died in typical convulsions in 5 minutes	
Control	207	0.1	1:50	66	0.05	Milk of Case 10 containing 0.005 c.c. of 1:10 egg white	Died in typical convulsions in 2 minutes	
Control	191	0.1	1:10	66	0.02	Milk of Case 10 containing 0.002 c.c. of 1:10 egg white	In 3 minutes sneezing, scratching, defecating. In 5 minutes on side in severe convulsions. In 10 minutes on feet again but convulsing. In 15 minutes quiet. Recovered	
Control	213	0.1	1:10	50	0.1	Of 1:1,000 dilution egg white	Died in 3 minutes with typical convulsions	

* Normal guinea-pig.

TABLE 2 (EXPERIMENT 2).—GUINEA-PIG SENSITIZED WITH BREAST MILK: SUBSEQUENT INJECTION WITH EGG WHITE INTRAVENOUSLY

Case	Guinea-Pig	Route of First Injection	Amount Breast Milk First Injection, C.c.	Description of Milk Used, i. e., Relation to Egg in Diet. Form in Which Eggs Taken Treatment of Milk	Interval Between Injections, Days	Amount Egg White Second Injection, C.c.	Dilution of Egg White	Reaction	Subsequent Injections and Necropsy Findings
1	19	Intraperitoneal	2	Taking 2 cooked eggs twice daily. Mixed 3 nursings. Milk not heated	33	0.3	1:5	No reaction	After 24 hrs. given 0.3 c.c. breast milk. Died in 10 min. in typical convulsions
2	20	Intraperitoneal	2	Taking 2 cooked eggs twice daily. Mixed 3 nursings. Milk not heated	33	0.3	1:5	No reaction	Given 0.15 c.c. breast milk intravenously next day. Mild convulsion, definite anaphylaxis but recovery
4	59	Intraperitoneal	2	Mother given whites of 4 raw eggs in milk. Two, five and eight hrs. after specimens mixed. Milk not heated	15	0.8	1:5	Shivered constantly 45 min. looking sick and irritable. No convulsive movements, hair not on end, no sneezing, urinating, or defecating	
5	69	Subcutaneous	6	Two hours, after 4 raw eggs. Milk pasteurized	24	0.2	1:5	No reaction	Necropsy showed pneumonia
5	70	Subcutaneous	6	Five hours, after 4 raw eggs. Milk pasteurized	24	0.2	1:5	Restless few minutes, then normal	Necropsy negative
5	83	Intraperitoneal	6	Two hours, after 4 raw eggs. Milk not heated	25	1.5	1:5	No reaction	After 2 days given 0.07 c.c. breast milk intrathecally. Def. reaction but recovered
5	93	Subcutaneous	11	Two hours, after 4 raw eggs. Milk pasteurized	23	1.0	1:5	No reaction	
5	94	Subcutaneous	6	Five hours, after 4 raw eggs. Milk not heated	23	1.5	1:5	Looked sick for 5 min. but normal thereafter	
5	96	Intraperitoneal	6	Five hours, after 4 raw eggs. Milk pasteurized.	25	1.0	1:5	No reaction	
5	114	Subcutaneous	8	Two hours, after 4 raw eggs. Milk pasteurized	23	1.0	1:10	No reaction	
5	115	Subcutaneous	8	Five hours, after 4 raw eggs. Milk pasteurized	23	1.0	1:10	No reaction	
6	72	Subcutaneous	15	Five hours, after 4 raw eggs. Milk pasteurized	33	0.6	1:5	No reaction	

7	82	Subcutaneous	10	Twenty hours, after 4 raw eggs. Milk not heated	17	1.0	1:5	Shivered, breathed fast and looked sick 2 hrs., then normal	After 2 days given 0.1 c.c. breast milk intrathecally. Def. reaction, but recovered
7	142	Subcutaneous	8	Eight hours, after 4 raw eggs. Milk not heated	14	1.0	1:5	No reaction	Next day given 0.07 c.c. boiled breast milk intrathecally. Severe convulsions with recovery
7 Control	143	Intraperitoneal	5	Eight hours, milk containing 0.1 of 1:10 egg white	17	1.0	1:5	Violent spasms, involuntary urination and death in 3 minutes	Necropsy showed distended lungs
8	196	Intraperitoneal	3	Two cooked eggs twice daily. Milk from 3 mixed nursings. Not heated	21	0.3	1:5	No reaction	
8	197	Subcutaneous	6	Two cooked eggs twice daily. Milk from 3 mixed nursings. Not heated	21	0.3	1:5	Shivered and gross rigors, irritable, and looked sick up to 2 hours	
8	197a	Intraperitoneal	5	Two cooked eggs twice daily. Milk from 3 mixed nursings. Not heated	21	0.5	1:5	No reaction	
9	232	Intraperitoneal	7	Four cooked eggs daily. 3½ (also 6½) hours, after 2 eggs. Milk not heated	21	0.5	1:10	No reaction	
9	233	Intraperitoneal	5	Four cooked eggs daily. 3½ (also 6½) hours, after 2 eggs. Milk not heated	21	0.5	1:10	No reaction	
9	234	Intraperitoneal	5	Four cooked eggs daily. 3½ (also 6½) hours, after 2 eggs. Milk not heated	21	0.5	1:10	No reaction	
9	235	Intraperitoneal	5	Four cooked eggs daily. 3½ (also 6½) hours, after 2 eggs. Milk not heated	21	0.5	1:10	No reaction	
Control	213	Intraperitoneal	0.1	1:10 dilution of egg white	50	0.1	1:1000	Died in 3 minutes with typical convulsions	
Control	218	.....	.....	Normal guinea-pig	..	0.3	1:5	No reaction	
Control	219	.....	.....	Normal guinea-pig	..	0.5	1:5	Slight shivering, then normal	
Control	165	.....	.....	Normal guinea-pig	..	1.5	1:10	No reaction	Necropsy negative
Control	168	.....	.....	Normal guinea-pig	.	1.5	1:5	Marked rigors first few minutes, then normal	Necropsy negative
Control	180	.....	.....	Normal guinea-pig	..	0.5	1:5	First 15 minutes looked irritable, breathed fast, scratched nose; then quiet and normal	Necropsy negative
Control	181	.....	.....	Normal guinea-pig	..	1.5	1:5	Shivered constantly, hair on end, few gross rigors, quiet in corner up to 2 hours	Necropsy negative
Control	182	.....	.....	Normal guinea-pig	..	1.0	1:5	No reaction, except excited and shivering	Necropsy negative

TABLE 3 (EXPERIMENT 3).—GUINEA-PIGS SENSITIZED WITH EGG WHITE INTRAPERITONEALLY: SUBSEQUENTLY KILLED AND REACTION OF UTERINE STRIP TO TEST BREAST MILK NOTED

Case	Guinea-Pig	Amount Sensitizing Dose Egg White Dilution	Dilution Egg White	Interval Before Killing Guinea-Pig	Number of Test Substances Added in Order	Description of Milk Used, i. e., Relation to Egg in Diet, Form in Which Eggs Taken, Treatment of Milk	Final Dilution of Substances Added to Ringer's Solution	Anaphylactic Response Shown by Immediate Contraction
4	32	0.3	1:10	28	(1)	Breast milk while on egg-free diet	1:100	None
					(2)	Breast milk 2 hours after four egg whites	1:100	None
6	41	0.1	1:5	53	(1)	Breast milk after egg-free diet	1:100	None
					(2)	Breast milk 2 hours after four egg whites	1:100	None
					(3)	Breast milk 5 hours after four egg whites	1:100	None
					(4)	Breast milk 5 hours after four egg whites (pasteurized)	1:100	None
8	67	0.1	1:10	34	(1)	Two cooked eggs night and morning. Milk taken 3 hours after eggs	1:100	None
					(2)	Same as (1) repeated	1:100	None
					(3)	Egg white	1:500	Marked
8	171	0.1	1:50	11	(1)	Taking two cooked eggs night and morning. Milk 3 hours after eggs	1:150	None
					(2)	Same, 6 hours after	1:150	None
					(3)	Same, 9 hours after	1:150	None
					(4)	Egg white	1:500	Marked
8	126	0 1	1:10	25	(1)	Taking two cooked eggs night and morning. Milk 3 hours after eggs	1:150	None
					(2)	Same, taken 6 hours after	1:150	None
					(3)	Same, taken 9 hours after	1:150	None
					(4)	Egg white	1:500	Marked
Control	5	0.4	1:40	93	...	Egg white	1:100	Marked
Control	27	0.2	1:10	19	(1)	Egg white	1:1,000	Marked
					(2)	Egg white	1:10,000	Very slight
Control	101	0.1	1:10	28	(1)	Egg white	1:1,000	Complete
					(2)	Breast milk (hospital supply)	1:100	None
					(3)	Egg white	1:1,000	None
					(4)	Egg white	1:1,000	None
Control	103 rt. 103 lft.	0.1	1:10	29	(1)	Egg white	1:1,000	Complete
					(2)	Breast milk (hospital supply)	1:100	None
					(3)	Breast milk (hospital supply)	1:100	None
					(4)	Egg white	1:500	Marked
Control	35*	...	....	..	(1)	Breast milk (hospital supply)	1:50	Slight
					(2)	Egg white	1:100	Marked
					(3)	Breast milk 1:50, containing egg white	1:500	Marked
Control	100*	...	....	..	(1)	Breast milk 2 hours after egg white	1:50	Moderate
					(2)	Breast milk 5 hours after four egg whites	1:50	Moderate
Control	128*	...	....	..	(1)	Egg white	1:250	None
					(2)	Breast milk (hospital supply)	1:100	None
Control	22	2.0	1:10	24	(1)	Egg white	1:50,000	Marked
					(2)	Egg white	1:100,000	Very slight

* Not sensitized.

TABLE 4 (EXPERIMENT 4).—GUINEA-PIGS SENSITIZED WITH TEST BREAST MILK: SUBSEQUENTLY KILLED AND REACTION OF UTERINE STRIP TO EGG WHITE NOTED

Case	Guinea-Pig	Route of Sensitization	Amount of Breast Milk	Description of Milk Used, i. e. Relation to Egg in Diet, Form in Which Egg Taken, Treatment of Milk	Interval Before Killing Guinea-Pig, Days	Number of Tests, in Order	Test Substance Added	Final Dilution in Ringer's Solution	Anaphylactic Response Shown by Immediate Contraction
5	104	Subcutaneous	4	Milk collected 2 hours after whites of four raw eggs. Not heated	33	(1)	Egg white	1:500	None
						(2)	Breast milk	1:100	Complete
5	107	Intraperitoneal	4	Milk collected 5 hours after four egg whites (raw). Milk heated to 65 for 20 minutes	33	(1)	Egg white	1:250	None
						(2)	Breast milk	1:500	Marked
5	120	Subcutaneous	6	Milk collected 5 hours after four egg whites (raw). Milk heated to 65 for 20 minutes	23	(1)	Egg white	1:1000	None
						(2)	Breast milk	1:100	Complete
5	105	Subcutaneous	4	Milk collected 5 hours after four raw egg whites. Milk not heated	33	(1)	Egg white	1:250	None
						(2)	Breast milk	1:250	Complete
6	106	Subcutaneous	10	Mother eating two to four cooked eggs a day. Milk not heated	21	(1)	Egg white	1:250	None
						(2)	Breast milk	1:500	Marked
7	130	Intraperitoneal	6	Milk collected 8 hours after four raw egg whites. Not heated	17	(1)	Egg white	1:250	None
						(2)	Boiled breast milk	1:100	Complete
7	132	Subcutaneous	8	Milk collected 20 hours after four raw egg whites	20	(1)	Egg white	1:200	None
						(2)	Breast milk	1:100	Complete
7	81	Subcutaneous	15	Milk collected 4 hours after eating four egg whites	22	(1)	Egg white	1:100	None
						(2)	Breast milk	1:250	Moderate
7 Control	125	Subcutaneous	8	Breast milk containing 0.1 c.c. of 1:10 egg white	18	(1)	Egg white	1:250	Moderate
						(2)	Breast milk	1:250	Complete
8	200	Subcutaneous	5	Three nursings mixed while on diet of two cooked eggs night and morning. Not heated	18	(1)	Egg white	1:1000	None
						(2)	Breast milk	1:200	Complete
8	198	Subcutaneous	5	Milk collected 3 hours after two cooked eggs. Taking four cooked eggs a day	21	Rt. horn (1)	Egg white	1:500	None
						(2)	Breast milk	1:200	Marked
						Lt. horn (1)	Egg white	1:500	None
						(2)	Breast milk	1:200	Complete
8	199	Subcutaneous	6	Taking two cooked eggs night and two morning. Milk collected 6 hours after last	21	(1)	Egg white	1:500	None
						(2)	Breast milk	1:200	Marked
Control	205†	.....	..	.....	18	(1)	Egg white	1:1000	Complete
Control	217	.....	..	Not sensitized	..	...	Breast milk	1:200	None

† Sensitized with 0.1 c.c. of 1:50 dilution egg white intraperitoneally.
For further controls see Experiment 3.

TABLE 5 (EXPERIMENT 5).—GUINEA-PIGS SENSITIZED WITH EGG WHITE: SUBSEQUENT INJECTION WITH BREAST MILK INTRATHECALLY, METHOD OF GAY AND SOUTHARD USED IN GUINEA-PIGS MARKED G. AND S.; OF BESREDKA IN THOSE MARKED BESR.

Case	Guinea-Pig	Amount of Egg White Dilution, C.c.	Dilution of Egg White	Interval Between Injections, Days	Amount Second Injection Breast Milk, C.c.	Description of Milk Used, i. e., Relation to Egg in Diet, Form in Which Eggs Taken, Treatment of Milk	Reaction	Subsequent Injections or Necropsy Findings
9	211	0.1	1:10	50	0.2 G and S	Mother taking two cooked eggs twice daily. Milk collected sterile 3½ hrs. after last eggs. Not heated	Unconscious 2 min., then up and quiet, looking sick. No spasms. Recovered	Died in typical convulsions following day after 0.1 c.c. of 1:10 egg white intravenously
9	145	0.1	1:10	50	0.1 Besr.	Mother taking two cooked eggs twice daily. Milk collected sterile 3½ hrs. after last eggs. Not heated	No reaction	
9	202	0.1	1:50	66	0.2 Besr.	Mother taking two cooked eggs twice daily. Milk collected sterile 3½ hrs. after last eggs. Not heated	Irritable and sick, scratching head and holding it on side 2 hours. Recovered	
9	176	0.1	1:10	66	0.1 Besr.	Mother taking two cooked eggs twice daily. Milk collected sterile 3½ hrs. after last eggs. Not heated	No reaction	
9	177	0.1	1:10	66	0.2 Besr.	Mother taking two cooked eggs twice daily. Milk collected sterile 3½ hrs. after last eggs. Not heated	Irritable, scratched head and sneezed ½ hour. Later nasal discharge and obstruction. Recovered	
9	175	0.1	1:10	66	0.1 Besr.	Mother taking two cooked eggs twice daily. Milk collected sterile 3½ hrs. after last eggs. Not heated	No reaction	
9	183	0.1	1:10	66	0.1 Besr.	Mother taking two cooked eggs twice daily. Milk collected sterile 3½ hrs. after last eggs. Not heated	No reaction	
9	178	0.1	1:10	66	0.1 Besr.	Mother taking two cooked eggs twice daily. Milk collected sterile 3½ hrs. after last eggs. Not heated	Restless ½ hour. Otherwise negative	
Control	213	0.1	1:10	50	Besr.	Second injection 0.1 c.c. of 1:1000 dilution of egg white	Looked little sick, shivered and occasionally scratched head	24 hours later given 0.5 c.c. of 1:10 egg white intravenously. Died in 3 min. in typical convulsions
Control	208	0.1	1:50	66	Besr.	Second injection 0.15 c.c. of 1:10 egg white dilution	Died in 7 minutes with typical convulsions	
Control	108	0.1	1:10	42	G and S	Second injection 0.1 c.c. of 1:5 egg white	Died in 6 minutes with typical convulsions	

Control	119	0.1	1:10	50	G and S	Second injection 0.05 c.c. of whole egg white	Died in 7 minutes with typical convulsions	
Control	179	0.1	1:10	66	0.05 Besr.	Same as in Case 9 tests but with 0.05 of 1:10 c.c. egg white added	Died in 2 minutes with typical convulsions	
Control	190	0.1	1:10	66	0.01 Besr.	Same as in Case 9 tests but containing 0.01 c.c. of 1:10 egg white	Died in 5 minutes with typical anaphylaxis	
Control	238*	...	....	..	0.01 Besr.	Milk of Case 9.....	Quiet, looked sick, held head to side. Otherwise negative	
Control	239*	...	....	..	0.1 Besr.	Milk of Case 9.....	No reaction	
Control	208*	...	....	..	0.25 Besr.	Mixed specimen of three feedings of another case on four eggs a day diet	In severe pain, crying, lying on side, very irritable 1½ hrs. Recovered	
Control	209*	...	....	..	0.25 Besr.	Mixed specimen of three feedings of another case on four eggs a day diet	Shivered, scratched head, cried, held head on side 2 hours	
Control	155*	...	....	..	0.1 G and S	Hospital mixed sample. This had been boiled	Very sick, after 5 minutes turned many circles to left. Then alternated periods of lying on side, breathing fast, and up about, restless and in pain. At times spasmodic contractures and true convulsions. Quiet after 4 hours	48 hours later, looking normal. Given 0.1 c.c. of egg white above opposite eye, intrathecally. Restless and irritable but otherwise negative
Control	156*	...	....	..	0.1 G and S	Hospital mixed sample. This had been boiled	Fairly well first 2 hours, then very sick with frequent convulsions for 2 hours	48 hours later, looking normal. Given 0.05 c.c. egg white intrathecally. No reaction
Control	157*	...	....	..	0.1 G and S	Hospital mixed sample. This had been boiled	Only held head on side first 1½ hours. Then fell over, convulsed, breathed deep. Soon up again, trying to walk, but again fell over. This lasted several hours	24 hours later, looking normal. Given 0.2 c.c. egg white. Immediately rolled sideways and acted much as day before. Recovered
Control	158*	...	....	..	0.2 G and S	Hospital mixed sample. This had been boiled	Looked sick 1 hour, then normal...	Following day given 0.2 c.c. egg white. Looked sick 1 hour, but recovered
Control	159*	...	....	..	0.3 G and S	Hospital mixed sample. This had been boiled	Made several revolutions, then looked sick 2 hours, then normal	Following day given 0.3 c.c. egg white intrathecally. Looked sick, otherwise negative
Control	153*	...	....	..	0.1 G and S	Hospital mixed sample. This had been boiled	Reacted just as Guinea-Pig 155	
Control	154*	...	....	..	0.1 G and S	Hospital mixed sample. This had been boiled	Reacted just as Guinea-Pig 157	

* Normal guinea-pig.

TABLE 6 (EXPERIMENT 6).—GUINEA-PIGS SENSITIZED WITH BREAST MILK: SUBSEQUENT INJECTION WITH EGG WHITE INTRATHECALLY, METHOD OF GAY AND SOUTHARD USED IN GUINEA-PIGS MARKED G. AND S.; OF BESREDKA IN THOSE MARKED BESR.

Case	Guinea-Pig	Route of First Injection	Amount of Breast Milk Sensitizing Injection, C.c.	Description of Milk Used, i. e., Relationship to Egg in Diet Form in Which Eggs Taken. Treatment of Milk	Interval Between Injections, Days	Amount of Second Injection Egg White, C.c.	Dilution of Second Injection in Saline	Reaction	Subsequent Injections or Necropsy Findings
5	65	Intraperitoneal	4	Mother given white of 4 eggs. Milk collected after 2 hours. Milk heated to 65 for 20 min.	37	0.1 G & S	1:5	First hour looked sick and shivered frequently. Next hour held head on side, otherwise well	24 hours later given 0.1 c.c. breast milk intrathecally. Again only looked sick. Necropsy negative except for openings through orbit
5'	68	Subcutaneous	6	Mother given white of 4 eggs. Milk collected after 2 hours. Milk heated to 65 for 20 min.	41	0.1 G & S	Whole egg white	Irritable first five minutes, then normal. No twitchings	24 hours later given 0.4 c.c. breast milk intravenously. Died in 4 minutes with convulsion. Necropsy showed lungs distended and opening above orbit
5	85	Subcutaneous	8	Mother given white of 4 eggs. Milk collected after 2 hours. Milk heated to 65 for 20 min.	36	0.05 G & S	Whole egg white	No reaction	48 hours later given 0.07 c.c. breast milk intrathecally. Severe convulsions, but recovery. Necropsy showed both openings into cranium
5	92	Subcutaneous	8	Same as above except milk collected 5 hours after egg	35	0.05 G & S	1:5	Looked sick and shivered. At end of ½ hour, temp. 104 F. Quiet in 4 hours. Dead next forenoon. No convulsions, no paralysis	Necropsy showed hemorrhage about opening above orbit
5 Control	90	Subcutaneous	8	Milk on egg-free diet. Milk not pasteurized	33	0.07 G & S	Whole egg white	No reaction	24 hours later given 1 c.c. of pasteurized milk intravenously. Had typical convulsions but recovered. Necropsy only showed opening into cranium
7	133	Subcutaneous	8	Mother given whites of 4 raw eggs. Four hours later milk collected. Not heated	17	0.1 G & S	Whole egg white	Ran about in circles, violently, 5 minutes; then quiet, but shivering and scratching head occasionally. After 2 hours persisted in holding head on side. Well next day	24 hours later given 0.5 c.c. boiled breast milk intravenously. Died in typical convulsions. Lungs distended. Opening into cranium seen
7 Control	144	Intraperitoneal	8 (containing 0.1 c.c. of 1:10 egg white)	Mother given whites of 4 raw eggs. Four hours later milk collected. Not heated	17	0.1 G & S	Whole egg white	After 10 minutes fell on side, breathing fast, and extremities in spasms. Quieted down after 25 minutes, but looked sick 2½ hours. Scratched nose violently, sneezed often	24 hours later given 0.1 c.c. of breast milk intrathecally. Fell on side and had severe convulsions for 20 minutes. Recovered. Necropsy showed only two openings into cranium

Control	134*	.....	...	.....	..	0.1 G & S	Whole egg white	Looked sick, held head on side. Otherwise no reaction	Necropsy showed opening into cranium
Control	153*	.....	...	.....	..	0.1 G & S	Whole egg white	No reaction	Necropsy showed opening into cranium
Control	154*	.....	...	.....	..	0.1 G & S	Whole egg white	No reaction	Necropsy showed opening into cranium
8	201	Subcutaneous	5	Mother eating 2 cooked eggs twice daily. Milk of mixed 3 feedings after last eggs, i. e., 3, 6 and 4 hours	24	0.25 Besr.	Whole egg white	Unconscious 5 minutes, then made several revolutions and sat quietly for a time, looking sick	Necropsy negative except for perforation through skull
Control	220*	.....	...	.....	..	0.25 Besr.	Whole egg white	Looked sick, but no reaction	
Control	221*	.....	...	.....	..	0.25 Besr.	Whole egg white	Very excited, running about cage, evidently in pain. No convulsion, but frequently twitched body	
Control	195*	.....	...	....	..	0.25 Besr.	Whole egg white	Very excited 5 minutes, then quiet. After ½ hour, started shivering and crying and working back extremities. Evidently in pain	
Control	203†	.....	...	.....	59	0.15 Besr.	1:10 egg white	In 3 minutes started deep breathing, in 5 minutes convulsions, and in 7 minutes died	Necropsy showed much distended lungs
Control	108‡	.....	...	.....	42	0.1 Besr.	1:5 egg white	Died in 6 minutes with typical convulsions	Necropsy showed lungs distended. Opening in cranium
Control	119‡	.....	...	.....	50	0.05 Besr.	Whole egg white	Died in 7 minutes with typical convulsions	Lungs distended. Opening in cranium

* Normal guinea-pig.
† Guinea-pig sensitized with 0.1 c.c. of 1:50 egg white solution, intraperitoneally.
‡ Sensitized with 0.1 c.c. of 1:10 egg white, intraperitoneally.

sensitizing normal guinea-pigs, so that the presence of breast milk did not inhibit, more than quantitatively at least, the action of the egg white.

The results of the foregoing experiments seemed especially strange when it is considered that Shannon had not only sensitized but had even shocked with much smaller doses and after much less egg; so it was determined to use another series, using the intrathecal route as he had done.

EXPERIMENT 5.—In this experiment egg sensitive guinea-pigs were tested with breast milk from Case 10 administered intrathecally. Seven of the injections were made through the vault of the skull, as originally advocated by Besredka,[8] one through the orbit, as suggested by Gay and Southard.[9] Some of these guinea-pigs showed absolutely no reactions, while others were very sick. Eleven normal controls were also used, and a number of these were very sick for some hours, in a few the symptoms being very violent. None of the symptoms in either case suggested anaphylaxis as it appeared in the six egg sensitive guinea-pigs given egg injections, but they sufficiently confused the picture to make the method absolutely unsuitable for milk injections.

EXPERIMENT 6.—Guinea-pigs were sensitized with breast milk as for Experiment 4, specimens from three different cases being used. Egg white was given through the orbit in five of these guinea-pigs, and by Besredka's original route in one. Eleven control guinea-pigs were also injected. The details of the reactions are given in the tables. The results are seen to be just as unsatisfactory as those obtained in Experiment 5, and the tests in no way suggest anaphylaxis.

Besredka advocated the intrathecal method because he believed that the anaphylactic reaction was due to a lesion produced by the sensitizing injection in the nervous system, but latent until the administration of the shock dose. By introducing the antigen into direct contact with the central nervous system he hoped to obtain maximum manifestations, and therefore, to be able to detect more minute quantities of antigen in an unknown specimen. This theory, however, has long since been abandoned, the work of Dale [7] and others having shown that the reaction is a local cellular one in the various tissues, independent of central nervous control. Furthermore, the method of Besredka was found to be less reliable than other methods because of the small dose permissable and the false reactions frequently produced by nonspecific central irritation. Gay and Southard [9] used the modification referred to above, which they believed permitted the introduction of larger doses, but since their time very little work has been done by experimenters with the intrathecal route. Pfeiffer,[10] in describing the methods used in anaphylactic

8. Besredka: Ann. de l'Inst. Pasteur **21**:117, 1907.

9. Gay, F. P., and Southard, E. E.: J. M. Research **21**:21, 1909.

10. Pfeiffer: Die Arbeitsmethoden bei Versuchen über Anaphylaxie; Abderhalden, Handbuch der Biologischen Arbeitsmethoden, Pt. 13, 2, 1.

investigation, only mentions the intrathecal route as one formerly used but employed very little in recent years. Furthermore, Besredka [11] himself states that the intravenous route is the most effective of all, and advocates only the subdural when using certain substances. He specifically warns against the injection of milk intrathecally unless heated to 100 C. because he has frequently seen guinea-pigs die within twenty-four hours after injections, independently of their anaphylactic state. It is to be noted that all of Shannon's guinea-pigs died after several hours. In our experience death in known anaphylaxis usually occurs within the first one-half hour, or recovery is complete. This fact in itself would render the route unsuitable for one half of Shannon's experiments, that is, shocking egg sensitive guinea-pigs with breast milk; for the milk as used by him had not been subjected to heat. In the other half of his experiments, in which an attempt was made to sensitize guinea-pigs to egg white by injection of breast milk, there is no indication for the use of this method, for properly prepared filtered dilutions of egg white should not contain cellular débris and do not cause coagulation when introduced intravenously, the two conditions under which Besredka advocated the use of the intrathecal route.

It seemed to me that if egg protein is demonstrable in breast milk when injected intrathecally, it should also be demonstrable by the intravenous route or by the Dale uterine strip method. Furthermore, owing to the foregoing considerations, I believe that the presence of this protein cannot be assumed to have been proved unless confirmed by one of these other methods. Wells [12] gives as one of the cardinal requirements for proof regarding the presence of a foreign protein that it be demonstrable by the uterine strip method. Shannon objects to the intravenous route because of the danger of embolism, but our cases, in many of which careful necropsies were performed and in none of which was evidence of embolism found, suggest that when skimmed milk or a filtered egg white dilution is used, this danger is not a real one. Furthermore, this argument could only apply to the interpretation of positive reactions, and could have no bearing upon the value of negative findings. As to the uterine strip method, Shannon mentions it, but does not say why he chose the intrathecal method in preference. The technic of the uterine strip test is far more time consuming, but the clean cut graphic results are well worth the additional labor. Certainly the tendency of the present day is to work only with the intravenous or the uterine strip methods when testing sensitized animals for the demonstration of antigen.

---

11. Besredka, A.: Anaphylaxis and Anti-Anaphylaxis and Their Experimental Foundations, St. Louis, C. V. Mosby Company, 1919.
12. Wells, H. G.: Physiol. Rev. **1**:44 (Jan.) 1921.

CONCLUSION

I believe that our experiments warrant the conclusion that egg white protein is not demonstrable in the breast milk of mothers by any of the methods at present at our command. I do not intend to suggest that such protein may not be present in infinitely small amounts, but knowing what small traces of egg white will sensitize guinea-pigs, I feel that the conclusion is warranted that infants must be extremely sensitive to be affected by the amounts which they receive from this source. The explanation, therefore, of the frequent finding of these positive reactions in exclusively breast fed infants has not as yet been given, and the problem calls for further investigation. My results, however, fail to suggest that breast milk is a medium for the transmission of antigen.

OXYGEN THERAPY IN PREMATURE BABIES WITH ANOXEMIA *

HARRY BAKWIN, M.D.

NEW YORK

By anoxemia is meant a condition in which the oxygen pressure in the systemic capillaries is abnormally diminished.[1] It is seen most frequently when the hemoglobin of the blood is less saturated with oxygen than normally. The difference between the amount of oxygen which the hemoglobin is capable of carrying (oxygen capacity) and the amount which it actually carries (oxygen content) is known as the oxygen unsaturation of the blood.

In normal adults Lundsgaard [2] found that the unsaturation of the venous blood varies from 2.7 to 9.0 c.c. of oxygen for each hundred cubic centimeters of blood, averaging 5.8 c.c. Our results with blood obtained from the longitudinal sinus of well infants (Table 1) are practically the same as those of Lundsgaard on blood from the median basilic vein of adults. The oxygen unsaturation varied from 5.1 to 8.3 c.c., averaging 6.7 c.c. Blood from a scalp vein is much more nearly saturated with oxygen than is longitudinal sinus blood. Arterial blood is normally about 95 per cent. saturated.[3]

METHODS

Oxygen capacity was calculated from the hemoglobin.[4] The oxygen content was determined by the Van Slyke and Stadie method.[5] The earlier estimations were made with the Van Slyke method.[6]

In cyanotic persons an increase in the oxygen unsaturation of the venous and arterial blood was demonstrated by Stadie [3] in pneumonia and by Harrop [7] in patients with uncompensated heart disease. Lunds-

* Received for publication, Nov. 21, 1922.

* From the Pediatric Service, New York Nursery and Child's Hospital and the Department of Pediatrics, Cornell University Medical College.

1. Haldane, J. S.: Respiration, Yale University Press, 1922, p. 124.
2. Lundsgaard, C.: Studies of Oxygen in the Venous Blood, I, J. Biol. Chem. **33**:133, 1918.
3. Stadie, W. C.: The Oxygen of the Arterial and Venous Blood in Pneumonia and Its Relation to Cyanosis, J. Exper. M. **30**:215 (Sept.) 1919.
4. Palmer, W. W.: The Colorimetric Determination of Hemoglobin, J. Biol. Chem. **33**:119, 1918.
5. Van Slyke, D. D., and Stadie, W. C.: The Determination of Gases of the Blood, J. Biol. Chem. **49**:1 (Nov.) 1921.
6. Van. Slyke, D. D.: The Gasometric Determination of the Oxygen and Hemoglobin of the Blood, J. Biol. Chem. **33**:127, 1918.
7. Harrop, G. A.: The Oxygen and Carbon Dioxid Content of the Arterial and Venous Blood in Normal Individuals and in Patients with Anemia and Heart Disease, J. Exper. M. **30**:241 (Sept.) 1919.

gaard,[8] working with venous blood alone, obtained similar results. All three observers agree that cyanosis is closely related to an increase in the oxygen unsaturation of the blood.

Cyanosis is, therefore, distinct evidence of anoxemia. It occurs frequently in premature babies and may be associated with a number of different conditions, such as cerebral hemorrhage, pneumonia and sepsis. The cases of cyanosis with which this paper is concerned, however, are those which occur so frequently during the first few days of life in prematurely born babies and for which no assignable cause can be found, except a few atelectatic patches in the lungs. In these babies cyanotic attacks start soon after birth and recur more or less frequently for several days. If the baby lives through this period the attacks usually cease. Death, however, is an all too frequent sequel.

TABLE 1.—THE OXYGEN UNSATURATION OF BLOOD FROM THE LONGITUDINAL SINUS OF WELL INFANTS

Case	Oxygen Capacity-Volume per Cent.	Oxygen Content-Volume per Cent.	Oxygen Unsaturation	
			Volume per Cent.	Percentage
1	15.1	7.9	7.2	48
2	15.1	9.2	5.9	39
3	16.4	11.3	5.1	45
4	14.4	8.5	5.9	41
5	16.5	9.1	7.4	45
6	14.9	6.7	8.2	55
7	15.1	7.2	7.9	52
8	13.7	6.6	7.1	52
9	13.9	7.5	6.4	46
10	18.0	11.3	6.7	37
11	20.2	13.0	7.2	36
12	14.1	8.9	5.2	37
13	16.7	10.9	5.8	35

The cyanosis in premature babies is usually extreme and is accompanied, as in adults, by an increase in the oxygen unsaturation of the blood (Compare case histories). During the cyanotic attack the respirations become progressively slower and finally cease. The heart also beats slower and becomes weaker; but it usually continues to beat for several minutes after respiration has ceased.

THE MODE OF PRODUCTION OF ANOXEMIA IN PREMATURE BABIES

According to Holt[9] expansion of the lungs of the new-born is a gradual process requiring several days for its completion. In small, frail babies full expansion of the lungs may be delayed for several weeks. As a consequence, the blood flowing through the walls of the collapsed alveoli is poorly or not at all oxygenated, whereas in the expanded

8. Lundsgaard, C.: Studies of Oxygen in Venous Blood, IV, J. Exper. M. **27**:219 (Sept.) 1918.

9. Holt, L. E.: Diseases of Children, 1919, p. 69.

portion of the lungs the blood is normally arterialized. The mixed arterial blood coming from the lungs, therefore, is incompletely oxygenated, and anoxemia results.

Evidence of the anoxemia in premature babies is found in the type of breathing so frequently seen in these babies. It is a matter of common clinical observation that the breathing in prematurely born infants is irregular both in rate and depth. Recently Eckstein and Rominger [10] obtained graphic records of the respiration. They found that it may be distinctly periodic in type and describe three varieties of periodicity. One type is that known as Cheyne-Stokes breathing, in which periods of hyperpnea are followed by periods of apnea. They have seen apneic periods lasting as long as ten seconds. In other cases, deep breaths alternate with shallow ones, the entire curve showing a wavelike rise and fall. The latter phenomenon they interpret as due to changes in the tone of the diaphragm. In a third type rapid, shallow respirations alternate with slow, deep ones.

According to Douglas and Haldane [11] periodic breathing is due to anoxemia. The stimulus of oxygen want, expressed physiologically by the decrease in the oxygen saturation of the blood, together with the carbon dioxid present, results in excitation of the respiratory center and hyperpnea. The hyperpnea relieves the oxygen want, and the breathing quiets down only to start up again when the oxygen deficiency reaches the stimulating point once more. Pembrey and Allen [12] have shown that Cheyne-Stokes breathing may be abolished by giving oxygen, thereby proving, Haldane believes, that this type of breathing is due to oxygen want.

EXPERIMENTAL STUDIES

The effect of oxygen on anoxemia in prematurely born babies was studied by comparing the saturation of the blood and the clinical condition before and after the administration of oxygen. The two babies selected for this study showed marked evidence of anoxemia. A large group of cases has been observed clinically during the past three years, but it did not seem advisable to make blood determinations.

Methods of Administering Oxygen to Babies.—In order that oxygen therapy may be of value, the oxygen must be properly given. The funnel method, which has been so widely used, is practically useless. Meltzer [13] estimated that by this method the inspired air is enriched

10. Eckstein, A., and Rominger, E.: Beiträge zur Physiologie und Pathologie der Atmung, Ztschr. f. Kinderh. **28**:1, 1921.

11. Douglas, C. G., and Haldane, J. S.: The Causes of Periodic or Cheyne-Stokes Breathing, J. Physiol. **38**:401 (June) 1909.

12. Pembrey, M. S., and Allen, R. W.: Observations Upon Cheyne-Stokes Respiration, J. Physiol. **32**:XVIII, 1905, (Proc. Physiol. Soc.)

13. Meltzer, S. J.: The Therapeutic Value of Oral Rhythmic Insufflation of Oxygen, J. A. M. A. **69**:1150 (Oct. 6) 1917.

by not more than 2 per cent. of oxygen. Haldane [14] devised an apparatus by which oxygen could be accurately and economically added to the inspired air. Oxygen was also given during the recent war with some success through a nasal catheter.[15] Excellent results have been obtained by various workers [16] with the oxygen chamber. Barach and Woodwell [17] found a rubber mouthpiece an effective means of giving oxygen.

In prematurely born infants oxygen may be given effectively by means of two fine rubber catheters inserted into the nostrils. The catheters are well lubricated and connected to the oxygen tank by means of a Y tube. The oxygen may also be given through a rubber tube about 1 cm. in diameter, inserted into the mouth. The rubber tube is held in position by a glass collar which fits snugly over the tube. The collar is held in place with tape, which is tied back of the baby's head. Since the small babies move very little, the collar and tube are easily kept in place. Such a collar eliminates the need of a nurse in constant attendance during the oxygen administration. Occasionally when oxygen is given in this way, it is swallowed, and the abdomen becomes distended. In such cases, of course, the oral route should be abandoned.[18]

REPORT OF CASES

CASE 1.—*History.*—A baby boy, who was delivered normally and weighed 1,690 gm., began to have attacks of cyanosis shortly after birth, the attacks usually occurring soon after a feeding. The blood oxygen determinations were made one day after birth. At this time the baby was deeply cyanotic, the heart rate 20 per minute and the rhythm regular. The breathing was very shallow and irregular. The physical examination otherwise was negative.

Treatment.—Oxygen was given through a tube inserted into the mouth. After a few minutes the baby became bright pink, the respirations became deeper and the heart sounds stronger. The baby continued to have attacks of cyanosis for the next few days, particularly after his feedings. He was treated each time with oxygen, to which he reacted promptly. He was discharged from the hospital cured, and when last seen was 6 months old and apparently well, except for slight malnutrition.

Comment.—In this case the oxygen unsaturation which was very high before the oxygen administration (14.8 c.c. for each hundred cubic

14. Haldane, J. S.: The Therapeutic Administration of Oxygen, Brit. M. J. **1**:181 (Feb. 10) 1917.

15. Stokes, quoted by Cummins: Proc. Roy. Med. Soc. **13**:59, 1920.

16. Barcroft, J.; Hunt, G. H., and Dufton, D.: The Treatment of Chronic Cases of Gas Poisoning by Continuous Oxygen Administration in Chambers, Quart. J. M. **13**:179, 1920. Shufflebotham, F., and Sowry, G. H.: Proc. Roy. Med. Soc. **13**:59, 1920. Stadie, W. C.: The Treatment of Anoxemia in Pneumonia in an Oxygen Chamber, J. Exper. M. **35**:337 (March) 1922.

17. Barach, A. L., and Woodwell, M. N.: Studies in Oxygen Therapy with Determination of Blood Gases, Arch. Int. Med. **28**:367 (Oct.) 1921.

18. These methods may also be used in older infants. Often, however, the babies struggle against the tubes. In these cases the oxygen may be given in a tent constructed from sheets.

centimeters) fell to normal (5.5 c.c.) after the oxygen was given. The results of the blood examinations are shown in Table 2.

CASE 2.—*History.*—A boy, the first child, was delivered normally and weighed 2,030 gm. Except for his small size he seemed normal. On the second day after birth it was noticed that he had attacks of cyanosis; at times he almost ceased to breathe. He was restored each time with counter irritation (mustard baths) and artificial respiration. The attacks became more and more frequent, and it was becoming increasingly difficult to revive him.

Examination.—The baby was seen during an attack on the third day. He was extremely cyanotic, spontaneous respiration having ceased. The heart rate was 15 per minute, and the sounds only faintly audible. There was sclero-edema of the skin over the abdomen and thighs.

Treatment.—Artificial respiration was used, but the apnea and cyanosis persisted. Oxygen was then given through a rubber tube in the mouth, and

TABLE 2.—INCREASE IN BLOOD OXYGEN OF CASE 1 AFTER THE ADMINISTRATION OF OXYGEN

	Oxygen Capacity, Volume per Cent.	Oxygen Content, Volume per Cent.	Oxygen Unsaturation, Volume per Cent.	Color
Before oxygen.....	27.9	13.1	14.8	Extreme cyanosis
After oxygen.....	27.9	22.4	5.5	Rosy pink

TABLE 3.—INCREASE IN BLOOD OXYGEN OF CASE 2 AFTER THE ADMINISTRATION OF OXYGEN

	Oxygen Capacity, Volume per Cent.	Oxygen Content, Volume per Cent.	Oxygen Unsaturation, Volume per Cent.	Color
Before oxygen.....	15.3	2.2	13.1	Deep cyanosis
After oxygen.....	15.3	7.6	7.7	Rosy pink

the artificial respiration continued. Within a few minutes the baby began to breathe spontaneously, the respirations becoming markedly periodic in type. As the oxygen was continued the baby became rosy pink in color, the respirations became more regular and the heart sounds improved in quality, the rate rising to 60. The oxygen unsaturation of blood from the longitudinal sinus fell from 13.1 to 7.7 c.c., which is within normal limits (Table 1). The results of the blood determinations are shown in Table 3.

The baby had several other attacks of cyanosis during the day and was revived each time with oxygen. The sclero-edema extended to the face and arms, and the baby died during the night. Necropsy was not permitted. There was no evidence of organic disease at any time, aside from the sclero-edema.

COMMENT

In the two cyanotic infants studied the oxygen unsaturation of the venous blood before treatment was markedly increased, indicating a severe degree of anoxemia. The administration of oxygen resulted, in both instances, in a prompt return of the oxygen saturation to normal. The cyanosis disappeared, abnormal respiration was abolished and the heart rate rose to normal. One of the two babies treated was 6 months

old when last seen and was apparently well, except for slight malnutrition. The other baby, who had sclero-edema at the time of treatment, died some time after the oxygen inhalations were discontinued.

During the past three years a large number of cyanotic premature infants have been treated with oxygen inhalations. The response to the oxygen is usually prompt, and but a few minutes are necessary before the cyanosis disappears and the character of the respirations changes. It is difficult to gage with any degree of accuracy the permanent value of oxygen to the babies. It did seem that, in general, when oxygen was administered early, the subsequent cyanotic attacks were fewer in number and more readily amenable to treatment.

With the methods employed (nasal catheters, mouth-tube), the oxygen could necessarily be given only over comparatively short periods of time. Though it was usually effective in remedying the immediate attacks of cyanosis, as a rule, the attacks recurred. In order that the full benefit of oxygen therapy may be obtained, it should be given over a long period of time. For this purpose the oxygen chamber is almost ideal.

SUMMARY AND CONCLUSIONS

1. The oxygen unsaturation of blood from the longitudinal sinus of well infants varies from 5.1 to 8.3 c.c., averaging 6.7 c.c.

2. The oxygen unsaturation of longitudinal sinus blood in two prematurely born babies with marked cyanosis was 14.8 and 13.1 c.c., respectively.

3. These two prematurely born babies with marked anoxemia, as indicated by the cyanosis and the increase in the oxygen unsaturation of the venous blood, were treated with oxygen inhalations. In both instances the cyanosis disappeared and the saturation of the venous blood rose to normal.

4. Oxygen may be given effectively to prematurely born babies through nasal catheters or through a rubber tube inserted into the mouth.

TOXEMIA OF SEVERE SUPERFICIAL BURNS IN CHILDREN *

BRUCE ROBERTSON, B.A., M.B. (Tor.)
AND
GLADYS BOYD, M.B.
TORONTO, CANADA

The very high mortality in cases of severe superficial burns and scalds in children has always occasioned grave concern. Against the mortality due to primary shock (which is comparable to primary traumatic shock) our resources are limited, and the nature of the injury is such that a much lower death rate from this cause is hardly to be expected.

An even higher mortality is encountered from toxic shock, and this condition we believe is more amenable to treatment than primary shock. However, under ordinary methods of treatment, there has been little reduction in the mortality due to toxemia, chiefly because attention

Analysis of 100 Consecutive Cases of Severe Burns and Scalds Admitted to the Wards of the Hospital for Sick Children. None of These Were Treated by Transfusion or Exsanguination Transfusion

	0-2 Yrs.	2-4 Yrs.	4-8 Yrs.	8-12 Yrs.
Recovered	16	31	11	7
Died * Primary shock	5	3	4	1
Died * Toxic shock	8	8	2	1
Total	29	42	17	9

* Three other children between 2 and 4 years died of bronchopneumonia, infection of burned area, and intestinal hemorrhage, respectively.

has been directed more to the problems of local treatment than to relief of the early toxemia which frequently results in death. Despite advances made in improving local applications for burned surfaces, the death rate is still distressingly high. We can only come to the conclusion that within certain limits the type of local dressing has little effect on the immediate issue. The treatment of toxemia or toxic shock merits our most thoughtful consideration, since in the earlier stages of the burn it is the most important factor influencing the success of the final result.

PROBLEMS ENCOUNTERED

The problems encountered early in cases of severe superficial burns in children are those of (*a*) primary shock and (*b*) toxemia or toxic shock.

* Received for publication, Dec. 15, 1922.
* From the Wards and Laboratories of the Hospital for Sick Children.

(*a*) *Primary Shock.*—When the primary shock is so intense that death may occur a few hours after injury, treatment directed toward relief of the shock is very disappointing, and the burn is usually so severe and extensive that it precludes the possibility of recovery either in the immediate or the remote future.

(*b*) *Toxemia or Toxic Shock.*—In a considerable number of cases the primary shock is mild or absent. Then follows an interval during which the general condition appears to be good—in fact, sometimes it is much better than the extent of the burn would warrant. But after the first twenty-four or forty-eight hours, the temperature begins to rise, and toxemia develops. The patient becomes drowsy, the pulse becomes more rapid and the circulation is somewhat depressed.

In cases going on to recovery the elevated temperature, and with it the toxemia, usually begins to subside about the fifth day, after which the problem becomes one of local treatment of the burn.

In the more severe cases, however, there is a greater rise in temperature, often to 106 F., and the toxemia is increased. Vomiting occurs as an early sign in fatal toxemia and becomes persistent. The pulse assumes a softer character, and the color tends to be dusky or livid, an evidence of capillary stasis. With the increasing toxemia, muscular twitchings occur, followed by convulsions. These usher in the final stage, and the patient dies after one or more convulsions.

The severity of the toxic symptoms corresponds to some extent with the area and depth of the burn. Second and third degree burns produce the most severe toxemia. There must, however, be individual differences, since we have seen comparatively small second and third degree burns produce fatal toxemia, while those of larger size have not been fatal. Age is an important factor: the younger the patient, the more severe are the symptoms with the same area involved. The situation of the burn also has some bearing on the severity of the symptoms. Those burns involving the chest and head usually produce more immediate and more severe symptoms than extremity burns.

Urinalysis.—In the great majority of burn cases the urine was found to be negative for albumin even in the stage of toxemia, although it was frequently reduced in amount at this time. In only a few cases was a trace of albumin found, and this was transitory.

Blood Findings.—In the early stages of the toxemia, the red blood cell count and hemoglobin were found to be slightly increased. This appears to be due only to concentration of the blood and is an evidence of the dehydrated condition of the tissues at this stage. The leukocyte count, however, may be increased, and we have seen it as high as 19,800 during the toxic stage. Increase in the leukocyte count several days after the burn is sustained is usually due to infection of the burned area.

In seven cases of burns, the nonprotein nitrogen content of the blood was estimated (G. B.) and was found to range from 42.9 to 99.0. The clinical application of these readings is not quite clear since in one case of recovery it reached 70.0, while in a fatal case it was 42.0. Again, in a case in which recovery followed treatment by exsanguination-transfusion, the reading was 42.9 at the height of the toxic stage, 46.21 five days later when the child had passed the critical stage, and 24.8, three weeks later, during convalescence.

It is probable that the increase of the nonprotein nitrogen is due to increased tissue destruction rather than to defective kidney elimination and is comparable to the findings of Rabinowitch [1] in intestinal obstruction. Our observations of the nonprotein nitrogen content in respect to burns are too few to warrant any conclusion as to prognostic importance.

From a purely clinical point of view, there seems to be no doubt that the burned tissues are responsible for the production of some toxin which is taken up by the blood stream. The appearance of toxic symptoms after the first twenty-four hours probably indicates that the damaged tissue must be in contact with living tissue before a toxic substance can be manufactured.

The nature of this toxin is not definitely known, but from the clinical symptoms, it would appear to be allied to the toxins produced in secondary wound shock and in intussusception. It differs from these toxins, however, in that it causes convulsions.

The treatment of these very severe cases of toxic shock in superficial burns in children offers a very definite problem. Every one admits, only to deplore, his helplessness when confronted with the case of a severely burned child in convulsions. In many of the cases the area of the burn would not constitute a surgical problem, but the toxic shock is likely to prove fatal.

RELIEF OF TOXEMIA

In casting about for some means of relieving the toxemia, two methods of attacking the problem were considered: (*a*) local treatment of the burn; (*b*) treatment of the toxemia, once it is established.

(*a*) The possibility of removing the damaged tissue either by excision or scrubbing was considered but was found to be impracticable, since in most of the cases the area was too large, or it involved regions such as the face, or the patients were admitted in the toxic stage.

The only chemical application which seemed to possess any value in diminishing the toxemia or retarding its onset was sodium bicarbonate in saturated solution. In conjunction with the local application, the

1. Rabinowitch, I. M.: Canad. M. A. J. **11**:163 (March) 1921.

drug was given by mouth to the limit of tolerance. By this means the bicarbonate content of the blood was found to be increased. Though its administration serves to decrease the so-called acidosis which is present and in this respect is only symptomatic treatment, its effect seemed to be favorable.

(*b*) It seemed to us that the simplest and quickest way of overcoming the toxin in the blood was to remove it. We assumed that removal of a sufficient quantity of blood might give the patient a chance to overcome further accessions of toxin. The freshly injected adult blood, even if it did not affect the toxin directly, would at least supply fresh nourishment to the tissues and help to reestablish a normal balance in the blood.

The assumption was not altogether theoretical, since we had had two burned patients who had convulsions and had recovered following straight blood transfusion.

To put into effect this idea, the operation of "exsanguination-transfusion" was devised in this hospital. The object was to withdraw a very much greater quantity of the patient's blood than could be obtained by simple venesection and to replace this with fresh adult blood. Briefly stated, the operation consists in the initial withdrawal of blood from the patient's longitudinal sinus or femoral vein until the limit of safety is reached. The transfusion is then commenced in an elbow vein. Withdrawal of the patient's blood and injection of fresh blood are then carried on simultaneously until the amount withdrawn is slightly less than the amount available for transfusion. The withdrawal is then discontinued and the remainder of available blood injected. The amount of blood withdrawn has ranged from 200 c.c. in an infant, up to 500 c.c. in a child of 3 years of age. It is obvious after the transfusion begins that a small but increasing percentage of the transfused blood is withdrawn. Notwithstanding this, the procedure in several cases appears to have turned the scales in favor of the patient. The technic is described in detail in a previous article.[2]

RESULTS

The results so far have been very encouraging. In ten cases of burns of the type described (i. e., with convulsions), two children received blood transfusion and eight were subjected to exsanguination-transfusion. Three of the latter died from burn toxemia. In the other seven cases, the burn toxemia was relieved.[3]

Under any method of treatment other than transfusion or exsanguination-transfusion, we have seen no burned patient recover after a

2. Robertson, B.: Canad. M. A. J. **11**:744 (Oct.) 1921.

3. One of these children died about two months later from a diphtheritic wound infection two weeks after operation for skin grafting on a different area.

convulsion has been precipitated as a result of the burn toxemia. In our opinion the operation of exsanguination-transfusion offers the better chance of recovery.

Coincident with the progress of the clinical work, experimental work was being carried out. Full details of these experiments will be published later, but as the results furnish some substantiation for the theory on which the treatment described above is based, a brief summary of our results and conclusions might be of interest.

Our experiments show that there is a substance produced in burned tissues (in larger quantities in extensive skin burns than in those of other tissues) which circulates in the blood, either in, or closely adsorbed to, the red blood cells and which causes the symptoms of toxic shock, and in some cases death. The toxic material is produced in increasing amounts following the burning of the tissue until from twenty-four to thirty-six hours after the injury. It is produced only as a result of burning living tissues. The toxin is most highly concentrated in solutions of corpuscles suitably treated and least in the blood serum.[4]

Chemically, this toxin consists of primary and secondary proteoses. Like snake venom, it is made up of two portions, a necrotoxic and a neurotoxic. The former is not destroyed by heat and is diffusible; the latter is thermolabile and colloidal.

We were unable to obtain any evidence of the production of antibodies against this poison. Katzeroff[5] recently reported the finding of such antibodies. His evidence is based on the beneficial effects of convalescent serum from burned patients in fourteen cases of toxic shock and not on biologic tests.

---

4. We have purposely not included in this paper the problems of secondary pyogenic infection of the burned area or the peculiar rash and temperature curve almost indistinguishable from scarlet fever which so frequently complicate the burn cases.

5. Katzeroff, A.: Rev. de chir., 1922, p. 60; abstr. J. A. M. A. **79**:507 (Aug. 5) 1922.

PROGRESS IN PEDIATRICS

A REVIEW OF THE LITERATURE ON THE BLOOD AND BLOOD DISEASES OF INFANTS AND CHILDREN FOR THE LAST FOUR YEARS (1918-1921) *

LEWIS WEBB HILL, M.D.

BOSTON

Although innumerable papers on the blood have appeared in the last few years, the proportion of really valuable contributions is small, and a great deal of the literature is unimportant from the reviewer's standpoint. The outstanding advances are an increase in knowledge of the blood chemistry in children, especially in the new-born, and in marasmic and intoxicated infants, and valuable contributions to our understanding of hemorrhagic disease of the new-born, aplastic anemia and alimentary anemia. There have also appeared important articles dealing with the classification of the "hemorrhagic diseases," and many contributions concerned with improved technic for transfusion.

THE BLOOD IN NEW-BORN INFANTS

Lucas,[1] Dearing, Hobler, Cox, Jones and Smith, in an extensive investigation of the blood of normal new-born infants, report the following: The blood in a large series of infants was studied from a few hours after birth up to the fourteenth day. The hemoglobin and red blood cells were found to show high values during the first few days, with a decided drop during the second week. Nucleated red cells were present in 52 per cent. of all cases on the first day, and in only 5 per cent. on the second day. There was also found to be a considerable variation in the size of the red cells for the first few days. The white blood cells varied from 19,200 on the first day to 13,200 on the twelfth day. The leukocytosis is due to increase in the number of polymorphonuclears during the first week; after which the lymphocytes begin gradually to increase. The average platelet count was from 305,000 on the first day to 266,000 on the eighth day. The platelets were not reduced in cases in which the coagulation was prolonged.

Blood Chemistry.—The urea and nonprotein nitrogen were about the same as in adults. The values for calcium were somewhat higher in the new-born than in older children, an average of 12.3 mg. for each hundred cubic centimeters of blood. (The normal value for older infants is from 10.8 to 11.5 mg. for each hundred cubic centimeters.)

* Received for publication, Dec. 15, 1922.

1. Lucas, W. P., et al.: Blood Studies in the New-Born, Am. J. Dis. Child. **22**:525 (Dec.) 1921.

"These calcium determinations show that in the blood of the new-born infant, calcium is rarely at fault in any problem related to hemorrhage, except in those cases of obstructive jaundice in which the calcium is bound by the bile salts and is, therefore, unavailable for entering into the process of coaggulation."

Coagulation.—In the first four days there is a definite prolongation in the coagulation time, whether hemorrhage occurs or not. This was prolonged in some cases to as long as thirty or forty minutes without the appearance of hemorrhage or increase in bleeding time. The average bleeding time is from one and one-half to three minutes.

Bile.—In seventy-two of ninety cases bilirubin was found in the plasma. Sedgwick [2] found that in the new-born the values for creatin plus creatinin and nonprotein nitrogen are high, corresponding to the high values for uric acid during that period. The creatinin and sugar values are essentially the same as the adult normal values, and the urea nitrogen is near the maximum normal value for adults.

Happ,[3] in 1919, studied the iso-agglutination reaction of 131 infants and children from birth to ten years. He found that at birth, and during the first month, iso-agglutination is rarely present, but the percentage of infants in whom the iso-agglutination group is established increases with age, so that after one year the group is usually established, and after two years it is always present as in adults.

Iso-agglutinins were found to be present in human milk, and the grouping was identical with that of the mother's blood.

Jones [4] studied the iso-agglutinins in the blood of new-born infants, and found that 78.7 per cent. of 197 specimens of blood could be placed definitely in one of the four recognized iso-agglutination groups. This percentage is much higher than any previously reported, and these results are probably dependent on a technic which permits the recognition of weak agglutinins.

Rodda,[5] in an important investigation on the coagulation time of the blood of new-born infants, describes a simple, practical method for determining this with small amounts of blood. This is of considerable value, as there was previously no very satisfactory method for use in small babies. The apparatus necessary consists of a spring lance, two 1½ inch watch glasses, and a No. 6 lead shot. The glasses and shot are cleaned with soap and water, followed by alcohol and ether. The heel

---

2. Sedgwick, J. P., and Ziegler, M. R.: Nitrogenous and Sugar Content, Am. J. Dis. Child. **19**:429 (June) 1920.

3. Happ, W. M.: J. Exper. Med. **31**:313 (March) 1920.

4. Jones, B. B.: Iso-Agglutinins in the Blood of the New-Born, Am. J. Dis. Child. **22**:586 (Dec.) 1921.

5. Rodda, F. C.: Determining Coagulation Time of Blood in the New-Born, Am. J. Dis. Child. **19**:268 (April) 1920.

of the infant is sponged with ether, a puncture is made with the lance blade, set at 0.5 cm. to produce a free flow of blood without the slightest pressure. A watch glass containing the shot receives the second drop of blood; a second watch glass is inverted over the first, and the watch glasses are gently tilted every thirty seconds until the shot no longer rolls, but is fixed in the clot. The end point is sharply defined, the shot is firmly embedded, so that the glass may be inverted without dislodging it. The greatest source of error is concerned with the blood flow. A small, slowly forming drop obtained by pressure clots very quickly. The blood flow must be free and must occur without pressure or squeezing. The first drop is discarded, the second drop only is used, and the time is reckoned from the moment when the first drop fell. No claim is made that the method is absolutely accurate, but the object is to find gross variations from a normal range.

By this method on 126 new-born infants within the first twenty-four hours of life, the average coagulation time was found to be seven minutes. A range of from four to ten minutes included 95 per cent. of the cases. Thus it may be said that with this method more than ten minutes means delayed coagulation. A bleeding time of from two to five minutes may be considered normal for the new-born infant. In the normal new-born infant there is found a tendency to prolongation of these times in the first few days.[6]

Schloss,[7] in a careful study of the blood in "intestinal intoxication" in infants, found that the nonprotein nitrogen was greatly increased, from 57 to 232 mg. per hundred cubic centimeters of blood. In normal infants it was found to be from 23 to 39 mg. per hundred cubic centimeters of blood. He found that there was no constant decrease of the blood plasma in relation to corpuscles, which proved that the high nonprotein nitrogen cannot be explained on the basis of increased blood concentration. He showed by a very painstaking series of experiments that there is, in these cases, a considerably decreased renal function, largely caused by dessication, and that the increased nonprotein nitrogen of the blood is largely due to this. He believes that "intestinal intoxication" and uremia are comparable conditions.

Utheim[8] studied the water content of the blood in various conditions in infancy. As a rule, the younger organism contains more water than the mature organism. Prematurely born infants have a high water content of the blood, and do not acquire the water content of a normal

6. Rodda, F. C.: The Coagulation Time of Blood in the New-Born, J. A. M. A. **75**:452 (Aug. 14) 1920.

7. Schloss, O. M.: Intestinal Intoxication in Infants, Am. J. Dis. Child. **15**:165 (March) 1918.

8. Utheim, K.: Study of Blood and Its Circulation in Normal Infants and in Infants Suffering from Chronic Nutritional Disturbance, Am. J. Dis. Child. **20**:366 (Nov.) 1920.

infant's blood until they are about 3 months of age. In athrepsia the water content is high and the protein content of the serum low. The high water content of the blood in athrepsia and prematurity might be considered one of the factors which explain their low immunity

The serum protein in normal infants ranges from 6 to 6.5 per cent. and remains at this level until the tenth or eleventh month, when it begins to rise, until, by the fifteenth month, it has reached the same level as in adults (about 8.7 per cent.). Infants with acute diarrhea and vomiting show a high percentage of serum protein, the result of blood concentration. Prematurely born infants and athreptics show a low serum protein, often as low as 4 per cent. There is also a low rate of blood flow, due sometimes to diminished blood volume, and sometimes to constriction of the small peripheral vessels. Marriott and Sisson [9] found that the average blood fat in infants was 0.68 per cent., somewhat higher than the figure of 0.59 per cent. for normal adults (Bloor). They found that (1) the blood fat is independent of the nutritional state of the infant. (2) Infants who are gaining show usually a distinctly higher blood fat than those whose weight is stationary or dropping. (3) Breast fed infants who are gaining weight have a high blood fat.

Greenthal [10] studied the fragility of the red blood cells to hypotonic salt solution. He found that (1) there is no distinctive reaction to the fragility test in the infectious diseases. (2) Fever per se has no effect on the fragility of the red cells. (3) In certain cases of infectious disease one may find a distinct increase of resistance. These cases are usually of great severity, and the prognosis is grave. It is conceivable that a compensatory mechanism causes the red blood cells to protect themselves against an injurious toxin by an increase in their resistance to hemolytic agents.

HEMORRHAGIC DISEASE OF THE NEW-BORN

Warwick [11] reports thirty-six routine necropsies performed on stillborn babies, or those dying soon after birth. In this series eighteen showed definite hemorrhages in the dura, over the brain, or in the ventricles. In eight of these cases, gross hemorrhages were found in other organs besides the brain. Is thus appears quite clear that in a fairly large percentage of cases showing intracranial hemorrhage such lesions are merely incidental to a general hemorrhagic diathesis.

Early recognition of decreased coagulability of the blood, and prompt treatment by injections of whole blood are to be desired.

---

9. Marriott and Sisson: Tr. Am. Pediat. Soc. **30,** 1920.
10. Greenthal, R. M., and O'Donnell, W. S.: Fragility of Red Blood Corpuscles in Infectious Diseases, Am. J. Dis. Child. **22**:212 (Aug.) 1921.
11. Warwick, M.: Am. J. M. Sc. **158**:95 (July) 1919.

ANEMIA AND THE "HEMORRHAGIC DISEASES"

Weill and Dufourt [12] describe "alimentary anemia" in infancy. The blood picture is characterized especially by a considerable deficiency of hemoglobin with but comparatively little drop in the red cell count. They believe that it is especially likely to occur in babies who start life with an insufficient supply of iron in the liver (prematurely born; twins) and in babies whose mothers had some wasting disease during pregnancy, such as tuberculosis, anemia or diabetes. It is probable that this type of anemia does not develop readily except in babies previously prepared for it by a poor condition of the mother. They quote Schmidt, who was unable to produce an anemia in experimental animals by feeding an iron poor diet, but the animals of the second generation were markedly anemic.

Schwarz and Rosenthal [13] describe what they call a "chlorotic type of anemia" in young infants, for which iron is a specific. Their cases correspond closely to those described by Weill and Dufourt. The disease may begin in early infancy but may not be apparent until the baby is 12 or 15 months old. It occurs especially in prematurely born infants and in twins. The hemoglobin is markedly diminished, but the red cell count rarely falls below 3,000,000. The color index is usually between 0.4 and 0.6. The anemia is usually cured by iron, which should be given in the form of iron containing foods as well as in the form of drugs.

Schwenke [14] discusses "severe anemia in early infancy." She recognizes two broad groups. The first group is characterized by a retardation of bodily and mental development, and shows a blood picture of pseudochlorosis; the second group shows, as the most striking sign, an enlarged spleen and a reversion of the blood morphology to an embryonic type. There were nine infants in the first group. All had been delicate and pale since birth. All but one were bottle fed, and had been overfed with milk, with but little solid food after the nursing period. They ranged in age from 1 to 3 years when first seen. Signs of rickets were insignificant or lacking, and the liver and spleen were not enlarged. The blood picture was characterized especially by a low hemoglobin percentage. In six cases it was from 15 to 25 per cent.; in three cases from 30 to 45 per cent. The red blood count was less diminished, and the white blood count and differential count were normal. The blood smear showed especially achromia, no polychromatophilia, and only very slight differences in size and shape of the

12. Weill, E., and Dufourt, A.: Anemia in Infants, Arch. de méd. d. enf. **24**:265 (May) 1921.
13. Schwarz, H., and Rosenthal, N.: Arch. Pediat. **37**:1 (Jan.) 1920.
14. Schwenke: Jahrb. f. Kinderh. **88**:181, 1918.

red cells, with but very few normoblasts. The platelets were present in normal numbers. In most of these cases there had been a good deal of difficulty in giving solid food when it was first started.

In most of Schwenke's cases there was congenital debility, either prematurity, or the babies were very small and feeble. All of the babies had been fed on practically nothing but milk. Rickets plays but little, if any, part in the etiology.

TREATMENT

Milk was considerably reduced in quantity (down to 10 ounces a day), and vegetables, fruit and meat were added to the diet. It usually took from three to six months to effect a cure. It was found that by greatly reducing milk, and adding vegetables and meat, a great deal of improvement resulted up to a certain point; then a standstill was likely to occur, which could not be influenced by iron, arsenic, or anything else. Schwenke believes that a one-sided milk diet is only part of the cause of the condition, and that congenital debility is far more important. It is a congenital dysfunction of the red blood forming organs. If other external agencies, such as infections, attack the child, the simple chlorotic type may take the form of a severe aplastic anemia, and the child may die. Only one necropsy was held in the series, and this showed a bone marrow relatively poor in cells, especially in myelocytes and nucleated reds.

Franzig [15] believes that the idea of Czerny's, which has also been advanced by Finkelstein, that the milk or milk fat has an active part in producing the alimentary type of anemia, has but little evidence to support it. He reports six cases of this type of anemia, the infants having been fed too long on a one-sided milk diet.

The children he treated received plenty of milk, well over 1½ ounces per pound of body weight, and a liberal caloric intake, furnished by the addition of sugar and starch. He added no vegetables as such, or meat, to the diet, but used a specially prepared extract of carrots, containing a great deal of iron. In most cases, after from four to ten weeks, there was a hemoglobin increase of from 20 to 30 per cent. He believes that the vegetable extract is much superior to vegetables without such preparation, as there is much less danger of producing digestive upsets.

Brinchmann [16] was able to produce an anemia of the chlorotic type in guinea-pigs by means of an iron poor diet. He found that by adding iron to the diet in medicinal form he was able to prevent the anemia, which is a rather significant fact, as it would indicate that in the

15. Franzig: Deutsch. med. Wchnschr. **47** (April 14) 1921.
16. Brinchmann, A.: Ztschr. f. Kinderh. **30**:158 (Sept. 5) 1921.

alimentary type of anemia in infancy inorganic iron may be a valuable prophylactic and therapeutic agent, a point which is in some dispute. He found that there was no difference in the anemia of prematurely born infants, whether they were naturally or artificially fed.

Lichtenstein [17] has made an interesting and important study of the iron metabolism in premature infants in an attempt to explain the anemia which they so frequently develop. According to him, the only investigation of iron metabolism in infancy in the literature which can be accepted as free from errors is that made by Langstein and Edelstein in 1914, who found that breast fed babies retained from 0.12 to 0.25 mg. of iron per day, on an intake of from 0.55 to 0.65 mg.

Lichtenstein studied thirty-six healthy, prematurely born infants at about the third month of extra-uterine life, and found an average hemoglobin of 40 per cent., with about three million red cells per cubic millimeter.

Careful metabolism experiments made on four prematurely born babies showed that there was a negative iron balance in each of about 0.25 mg. daily. These babies were all fed on human milk, and were doing well. He has shown definitely that in prematurely born babies the amount of iron excreted is greater than the amount taken in with the food; this loss, after a while, causes a chlorotic type of anemia of fairly severe degree. The negative iron balance is explained by the fact that in prematurely born babies there is not a sufficient reserve supply of iron in the liver, as this reserve is largely deposited in the last two months of pregnancy. Lichtenstein gave one of these babies 50 mg. of iron per day in the form of ferric chlorid, and found that instead of the previous negative iron balance there was a positive balance of 1.7 mg. per day, and he says that in giving iron as a drug it is undoubtedly true that only a very small portion of the iron given is absorbed, but inasmuch as the iron needs are so minute, this is likely to be enough.

Whipple, Hooper and Robscheit [18] extensively investigated the regeneration of red cells and hemoglobin following simple anemia in dogs, produced by hemorrhage and the influence of dietary factors on this regeneration. They bled dogs one-fourth of the determined blood volume on each of two successive days. They found that under carefully controlled experimental conditions a diet of mixed table scraps will effect complete blood regeneration (to normal) in from four to seven weeks. Under similar experimental conditions there will be little blood regeneration during a fasting period. During sugar diet periods the regeneration of hemoglobin and red cells is distinctly less than during

17. Lichtenstein: Acta Pediat. **1**:2, 1921.

18. Whipple, G. H., Hooper, C. W., and Robscheit, I. S.: Am. J. Physiol. **53**:151 (Sept.) 1920.

fasting periods. They explain this by the fact that during fasting a certain amount of body protein is broken down to supply the metabolic needs of the body, and that part of this is probably used in blood regeneration, but that during sugar feeding the carbohydrate intake acts as a nitrogen sparer, and not so much body protein is made available for purposes of blood regeneration.

A diet of dried white bread and skimmed milk may cause a slow steady gain in blood pigment volume from week to week, and a liberal diet of this type, sufficient to maintain body weight, will often suffice for complete blood regeneration. Rice, potatoes and skimmed milk may be classed with bread and milk. Cooked liver and meat are most efficient, when added to the standard diet, in causing increased blood regeneration, and a diet of this type will bring back the blood to normal within three weeks.

Iron in the form of pills of ferrous carbonate (Blaud's pills) was found to be entirely without effect on blood regeneration, nor were ferric citrate or ovoferrin found to exert any appreciable influence.

TABLE 1.—BLOOD DIAGNOSIS (OTTENBERG)

	Coagulation	Bleeding Time	Platelets
Hemophilia	Greatly prolonged	Normal or plus	Normal
Hemorrhage of new-born	Greatly prolonged	Prolonged	
Purpura hemorrhagica	Normal	Greatly prolonged	Greatly decreased
Purpura, secondary to			
1. Jaundice	Prolonged		
2. Chloroform	Prolonged		
3. Scurvy	Normal	Normal	Normal
Purpura simplex Arthritic purpura Visceral purpura	Normal	Normal	Normal

Iron in the form of hemoglobin may be concerned in the somewhat favorable action observed after feeding this by mouth. But the chances are that the iron is less important than the pyrrol ring. Arsenic was also found to be inert. No drug has been tested which can compare with the factors in meat for stimulating a rapid regeneration of blood following hemorrhage.

"These carefully controlled experiments give no support to the time honored custom of administering iron and certain other drugs in simple anemia. The burden of proof rests with those who claim that any given drug is potent under such conditions. . . . Those who claim that iron is a potent drug must exclude the food factors which are known to be concerned before they can prefer any objection to these statements." [19]

19. It must be remembered that this work was done with one sort of anemia —that due to massive hemorrhage—and that it does not necessarily apply, and indeed probably does not apply, to the "alimentary anemia" which has already been discussed, a totally different form of anemia, probably directly dependent on an iron deficiency.—L. W. H.

Ottenberg [20] gives in clear tabular form some of the differences between the various "hemorrhagic diseases." He also describes the following simple method of counting the blood platelets: "The blood is diluted in the counter exactly as for making a red count. It is then placed in the counting chamber and let stand for at least ten minutes in order to allow the platelets to settle. They are then counted in the same manner as the red cells, except that on account of their relative scarcity about ten times as many squares ought to be counted."

Aplastic Anemia.—Smith [21] collected in the literature from 1888 to December, 1918, sixty-four cases of this rare disease. It is a most severe disease, characterized by its rapid and progressively fatal course. No patients have been known to recover. Hemorrhagic manifestations,

TABLE 2.—ARCHIBALD'S DIAGNOSTIC POINTS BETWEEN APLASTIC ANEMIA AND PERNICIOUS ANEMIA

	Aplastic Anemia	Pernicious Anemia
Onset	Usually early in life	In adult life
Etiology	Unknown	Unknown
Progress	Acute and rapid	Slow and chronic
Remissions	None	Remissions present
Hemorrhages and petechiae	Common	Not common
Fever	Usually present	Usually absent
Mouth	Not sore	Sore
Numbness	Absent	Present
Color index	Low	High
Leukopenia	Yes	Yes
Small lymphocytes	Relative increase	Relative increase
Regeneration	No evidence	Evidence
Blasts	Absent	Present
Hemolysis	No evidence	Evidence
Bone marrow	Aplastic	Hyperplastic

such as nosebleed or purpura, are almost always associated with it. There is usually a tremendous degree of anemia, and very large drops in the red cell count may take place with extraordinary rapidity. The skin may or may not show pigmentation.

No definite etiology has yet been found. Archibald [22] believes that there are borderline cases between aplastic and pernicious anemia, and that some relation may exist between the two conditions. Some of the reported cases show an extreme aplastic condition of the bone-marrow, with little or no hemolysis, while others show hemolysis as well as a failure to regenerate blood cells.

The differences between aplastic and pernicious anemia are shown in Table 2.

20. Ottenberg, R.: M. Clinics N. America **2**:289 (July) 1918.
21. Smith, L. W.: Aplastic Anemia, Am. J. Dis. Child. **17**:174 (March) 1919.
22. Archibald, A.: M. Clinics N. America **3**:757 (Nov.) 1919.

Larrabee,[23] in an excellent discussion, says that the especial significance of aplastic anemia is a poor function on the part of the bone marrow, failing to produce a normal number of red blood cells.

The view has often been expressed that aplastic anemia is merely pernicious anemia without regenerative changes in the marrow. Larrabee does not agree with this, and thinks that there is more reason for believing that aplastic anemia may result from some of the factors usually causing ordinary secondary anemia. Hemorrhage or severe sepsis may result in exhaustion of the marrow. Poisons, such as benzene, may produce an anemia closely allied to aplastic anemia. In leukemia, also, one may find similar changes. These are all secondary forms of aplastic anemia, but there is a large group in which the function of the marrow is inhibited from unknown causes, and the patient becomes anemic from the ordinary process of blood destruction.

The most striking features of the disease are the anemia and the marked tendency to bleed. The platelets are much decreased. Whereas the normal count is about 300,000, they may be reduced to only a few thousand. Coagulation time is prolonged, and the clot, when it does form, does not retract. The bleeding time is also prolonged. Subcutaneous hemorrhages are present in almost every case. The blood picture is definite: the red cells and hemoglobin are greatly diminished, usually in about the same proportion. Abnormalities in size and shape are slight, and nucleated red cells are usually absent. The white cells are also decreased, and the deficiency is confined to the polymorphonuclear neutrophils, eosinophils and mast cells.

Besides aplastic anemia there are other conditions in which the marrow is partially deficient. Purpura hemorrhagica is the most important of these. This is probably a form of aplasia involving only the platelet producing function of the bone marrow. In purpura hemorrhagica there is no aplasia either of the red or white cell producing functions. In this disease the aplasia is therefore only partial, and, if platelets are supplied by a transfusion, the hemorrhages are usually stopped for a few days. It is probable that some patients will recover entirely.

Musser[24] believes that aplastic anemia is an anemia secondary to primary bone marrow changes, and is not the result of hemolysis. It is a type of anemia in which the blood changes are dependent entirely on changes in the marrow, which, in turn, probably becomes pathologic as a result of some toxin which has a predilection for it. It is quite different from the so-called pernicious type of anemia, in which the bone

23. Larrabee, R. C.: Aplastic Anemia and Related Conditions, J. A. M. A. **75**:1632 (Dec. 11) 1920.

24. Musser, J. H., Jr.: M. Clinics N. America **3**:1403 (March) 1920.

marrow is red and hyperplastic and is presumably putting out a large number of cells, which are rapidly destroyed.

Rosenfield [25] reports two cases of idiopathic purpura with extensive and repeated hemorrhages into the capsule of the joints, a rather rare condition.

Larrabee [26] discusses the treatment of the "hemorrhagic diseases" (purpura, hemophilia, etc.). Appropriate treatment will almost always stop the bleeding, but the control is only temporary: the tendency to bleed will sooner or later recur, except in the few cases in which the causative disease is itself temporary. Local applications of styptics, such as ferric chlorid and epinephrin, are not very satisfactory. Cephalic and other tissue extracts are of somewhat more value. Calcium salts are of value only when the hemorrhage is due to calcium deficiency (chronic obstructive jaundice).

Fresh animal serum contains prothrombin, the coagulating element which is deficient in hemophilia and in hemorrhagic disease of the new-born. It does not contain platelets, and so is valueless in hemorrhagic purpura and other diseases in which the bleeding is due to platelet deficiency. Old serum is absolutely valueless. Transfusion with whole blood is the best thing for almost all of these cases, as it supplies all the elements for coagulation. If facilities for transfusion are not at hand, intramuscular injections of the whole blood are valuable, especially in the tissues near the bleeding area.

Condat [27] reports a case of "pernicious" anemia in a girl, aged 12 years. The hemoglobin was 25 per cent.; the red blood count, 780,000; the white count, 6,560. No nucleated red cells were seen, and no mention is made of the platelets. The general size of the red blood cells was large, and there was slight anisocytosis, otherwise there was nothing remarkable. The patient died, and there was no necropsy.[28]

Ward [29] discusses the so-called von Jaksch type of anemia. He believes that in this disease we are dealing with a hyperplastic process in the lymphoid tissues similar to leukemia, but on a lower plane. In infants with rickets, which is almost universally present in this type of anemia, there is a peculiar liability for the response to chronic infections to assume the characteristics of a leukemia rather than to show the more usual polymorphonuclear leukocytosis. Von Jaksch anemia may be regarded as a secondary or symptomatic leukemia, and represents the reaction of the blood forming tissues of rachitic infants to an organism

25. Rosenfield: Boston M. & S. J. **183**:89 (Aug. 5) 1920.
26. Larrabee, R. C.: Boston M. & S. J. **183**:151 (Aug. 5) 1920.
27. Condat: Arch. de méd. d. enf. **24**:676 (Nov.) 1921.
28. This cannot be accepted as an authentic case of pernicious anemia, as there is not enough evidence to rule out aplastic anemia. It was possibly a case of the latter disease.
29. Ward, G.: Brit. J. Dis. Child. **15**:101 (April-June) 1918.

or organisms which can produce the disease in a favorable soil. It is one of those progressive morbid processes which are sometimes termed symptoms, sometimes diseases.

The combination of a large spleen and anemia does not justify the diagnosis except when it occurs in infancy and is associated with rickets and infections. The conditions present in rickets are in some way responsible for the reaction to infection taking the form it does. Infection is the exciting factor, rickets the predisposing factor.

Evans and Happ,[30] after an excellent study of secondary anemia in young children, with and without enlargement of the spleen, believe that the so-called "von Jaksch disease," or "anemia infantum pseudoleukaemica" is not a disease of itself, but represents merely a secondary anemia due in most cases to unknown causes. The enlargement of the spleen, which may or may not be present, represents a peculiarity of reaction of the infant's hematopoietic system to anemia, and is not of particular significance. Neither is the mononuclear leukocytosis, which is likely to be present, significant, and likewise represents a special reaction on the part of the infant to anemia. It certainly bears no relationship to leukemia.

"The symptom complex usually called 'von Jaksch disease' can best be interpreted as the peculiar type of reaction on the part of the infant to the presence of a factor producing anemia, and should not be regarded as a disease *sui generis*. Rickets is frequently associated with *it*, but the condition is probably not caused by rickets.

Amesse [31] reports a case of Banti's disease in a boy, aged 6 years, who was cured by splenectomy. He made a good operative recovery, and soon after the hemoglobin rose from 30 per cent. to 70 per cent. and the red count became normal.

Canelli,[32] who has had much experience with Banti's disease in children, says that hemorrhage is one of the earliest symptoms, that glandular swelling is often present and that splenectomy is most beneficial when undertaken early in the course of the disease.

Leukemia.—There is nothing essentially new in the etiology or treatment of lymphatic leukemia, the usual form of this disease in childhood. It is uniformly fatal, usually in a short period of time, although transfusions may prolong the course.

Martelli [33] believes that there is a condition of infection of some sort usually associated with leukemia and that the disease is probably brought about by chronic infection.

---

30. Evans, F. A., and Happ, W. M.: Bull. Johns Hopkins Hosp. **33**:1 (Jan.) 1922.
31. Amesse, J. W.: Colorado Med. **17**:12 (Jan.) 1920.
32. Canelli, A. F.: Pediatria **29**:832 (Sept. 15) 1921.
33. Martelli, C. D.: Pediatria **26**:15 (Jan.) 1918.

In forty-five cases of acute leukemia he found an associated tuberculosis, syphilis, malaria, or pyogenic infection.

Baastrup [34] reports three cases of acute leukemia in which at, or before, the onset there was severe mouth infection, with tonsillitis and stomatitis. He believes that the disease is of infectious origin, and that its course often closely resembles that of acute sepsis.

Smith [35] reports what is probably the youngest case of lymphatic leukemia on record. A baby, 3 weeks old, began to vomit and to show loss of weight. Physical examination revealed an enlarged axillary lymph node, as large as a walnut, which the mother said had been present since birth. The spleen was also considerably enlarged, and there were ten or twelve purpuric spots scattered over the body. The white blood count was 189,000, 97 per cent. of which were lymphocytes.

GAUCHER'S DISEASE

Foot and Ladd [36] report a case of this rare disease lacking many of the usual symptoms. There were enlarged spleen, pain in the abdomen and legs, and profuse sweating. Splenectomy was performed, with most gratifying immediate results. "We know that the disease is fatal if untreated, or if treated by any other means than radical operation; we likewise know that splenectomy will afford very marked temporary relief from symptoms and improvement in general health. With these facts in view early splenectomy is therefore the treatment to be for the present recommended."

TRANSFUSION

In the last four years 229 articles dealing with various aspects of transfusion have appeared. The technic has been considerably improved, and transfusion has become a much more widely used procedure than it was five years ago. This is due to simplification of technic, so that it may be done with rather simple apparatus, and comparatively slight surgical experience. There are three methods of transfusion in general use, the citrate method, the syringe-cannula method of Lindeman, and the paraffin tube method of Kimpton and Brown, which was one of the earliest simplified methods of transfusion to be described. From a study of the literature, it is apparent that at the present time the citrate method (adding sodium citrate to the blood in order to prevent clotting) is by far the most popular, and although it unquestionably has certain disadvantages, its ease of performance makes it much more practical for the average medical man, and much more widely applicable than either of the other methods.

---

34. Baastrup: Ugesk. f. Læger **80**:5 (Jan. 3) 1918.
35. Smith, L. W.: Acute Leukemia in an Infant, Am. J. Dis. Child. **21**:163 (Feb.) 1921.
36. Foot, N. C., and Ladd, W. E.: Gaucher's Splenomegaly, Am. J. Dis. Child. **21**:426 (May) 1921.

Koplik [37] discusses the indications for transfusion. In the new-born they are as follows: (1) uncontrolled hemorrhage from wounds, umbilicus or scalp hematoma; (2) frank melena; (3) concealed melena in which the outward objective signs of hemorrhage are slight, but in which the evidence of internal hemorrhage is great; (4) cases of severe and continued hemorrhage in the new-born caused by surgical wounds, such as circumcision.

Koplik believes in immediate transfusion for hemorrhagic disease of the new-born, rather than subcutaneous injection of blood. He emphasizes cases in which the subcutaneous injection of blood has failed, and transfusion has had to be resorted to.

Kimpton [38] discusses his experience with transfusion in more than 200 cases. He is a strong advocate of the paraffin tube method, using uncitrated blood. He calls especial attention to the possibility of anaphylaxis, even after the bloods of the recipient and donor have been tested for agglutination and hemolysis, and reports one death due to this.

There is no condition in which transfusion, used at the right time, gives better results than it does in hemorrhagic disease of the new-born.

Kimpton believes that transfusion should be performed immediately in a baby having enough hemorrhage to show clinically because one never knows when further hemorrhage may suddenly occur, and prove fatal. From 60 to 100 c.c. of blood is enough. Kimpton has never seen an untoward reaction of any sort due to transfusion in the new-born, and does not believe that it is necessary to group the bloods preliminary to transfusion. He has used the father as a donor in nearly all cases, without previous blood grouping.

In hemophilia the mother is not necessarily contraindicated as a donor, provided agglutination tests are made. He does not believe in the citrate method of transfusion, largely on account of the much greater liability to untoward reaction, whereas with the paraffin tube method, using citrated blood, the occurrence of reaction is very rare. He describes the technic of this method in detail.

One of the disadvantages of most of the agglutination tests is that sample serums of Types II and III are necessary, which is a considerable disadvantage from the standpoint of the general practitioner.

Kimpton describes a very simple test for agglutination, which can easily be performed at the bedside.

Donor's Blood.—(1) From 2 to 3 drops of blood plus 0.5 per cent. oxalate (or salt) solution = corpuscles. (2) From 2 to 3 drops of blood plus distilled water = serum.

37. Koplik, Henry: Tr. Am. Pediat. Soc. **31**:96, 1919.
38. Kimpton, A. R.: Boston M. & S. J. **178**:351 (March 14) 1918.

Recipient's Blood.—(3) From 2 to 3 drops of blood plus 0.5 per cent. oxalate (or salt) solution = corpuscles; (4) from 2 to 3 drops of blood plus distilled water = serum. The oxalate or salt solution keeps the corpuscles free, and the water lakes the corpuscles and gives a serum.

On a hanging drop slide place one drop of Solution 1 and one drop of Solution 4, the donor's corpuscles and the recipient's serum. The procedure is repeated with Solutions 2 and 3, the donor's serum and the recipient's corpuscles.

These are observed for from twenty to thirty minutes with the microscope or hand lens for clumping. If clumping is marked, this may be seen with the naked eye.

Marble [39] recommends the citrate method. The most important point of technic is that the blood must pass easily and quickly into the citrate solution and be mixed immediately with it before coagulation begins. If known type serums are not available for typing—and they would not be outside of large hospitals—the following method is practical and simple. Blood is drawn from the recipient the same as for a Wassermann test. It is allowed to clot and the serum to separate. The serum is pipetted off and centrifuged until it is clear. Then, 3.8 per cent. sodium citrate solution, in the proportion of 1 part to 10 parts of serum, is added. This mixture is used as a type serum, and is mixed with blood from various donors, rejecting those that agglutinate. Marble calls especial attention to the fact that in the citrate method it is not necessary to cut down on a vein, and he believes that this advantage offsets any disadvantages that the method may possess.

Karsner [40] describes the Lee method of determining blood groups. For this test it is necessary to have the serum of members of Groups II and III. A platinum loopful of each one of these serums is placed on a slide, and to each drop is added either an equal amount of whole blood, or blood placed in 1 per cent. sodium citrate or physiologic solution of sodium chlorid. The reading of the agglutination is made under the microscope, and is usually completed in from five to fifteen minutes. If both drops show agglutination, the blood is in Group I; if neither drop shows agglutination, it is in Group IV; and if one drop shows agglutination and the other does not, it belongs to the group in which there is no agglutination.

The grouping of Lee is as follows:

Cells of Groups		Serums of Groups		
1	—	++*	+++	++++
2	—	—	+	+
3	—	+	—	+
4	—	—	—	—

* The plus sign indicates agglutination or hemolysis.

39. Marble, H. C.: Boston M. & S. J. **182**:153 (Feb. 5) 1920.

40. Karsner, H. T.: Transfusion with Tested Bloods, J. A. M. A. **70**:769 (March 16) 1918.

According to Lee (quoted by Karsner) the following is the best method of procedure for testing, if serums from known groups are not available.

A small amount of blood is collected from a patient and is allowed to clot. The serum is then obtained. One drop of this serum is placed on a slide and mixed with a drop of a suspension of blood of the donor taken in 1.5 per cent. citrate solution. The reaction will appear in a few moments, and is best examined under the microscope. In the event of a positive reaction, marked agglutination will be evident. The agglutination will also be evident macroscopically.

In the event of a negative reaction, it is a wise precaution to raise the coverglass, and, after making sure that the serum and cells are well mixed, to examine the preparation again. If the test is negative, transfusion may be regarded as being entirely safe.

According to Karsner, from an analysis of a grouping of 1,000 bloods, the chances per thousand bloods of a member of any group having a suitable donor in case the bloods are not tested, are as follows: Group I, 493 bloods; Group II, 886 bloods; Group III, 545 bloods; Group IV, 462 bloods. According to these and other statistics, the chances of any member of whatever group having a successful transfusion if the bloods are not tested is 649 in 1,000.

Drinker and Brittingham,[41] in eighty-three transfusions by the citrate method, noted a rise of temperature of 2 to 3 degrees in 60 per cent. of the cases. The syringe cannula and the paraffined tube methods are much less likely to give reactions than the citrate method. They believe that the plasma is nontoxic, and that one element in the appearance of toxicity is in the platelets, which begin to become abnormal as soon as they leave the blood vessels. Citrated plasma freed from formed elements is nontoxic. The marked whole cell content of blood is uniformly toxic.

It is probable that three elements make up the total of reactions in citrate transfusions: (1) very rare gross incompatibilities; (2) changes in the platelets, part of the process of coagulation, and (3) direct action of the sodium citrate on red cells, promoting hemolysis.

Unger [42] says that the more nearly one uses blood as it exists within the vessels of the donor, the nearer one attains ideal conditions. He is in favor of unmodified blood, and believes that the percentage of severe reactions is much less than when modified (citrated) blood is used. In his series of transfusions with unmodified blood, febrile reactions occurred in only 10 per cent. of all cases as against 60 per cent. of

41. Drinker, C. K., and Brittingham, H. H.: Transfusion Reaction, Arch. Int. Med. **23**:133 (Feb.) 1919.

42. Unger, L. J.: Therapeutic Aspect of Blood Transfusion, J. A. M. A. **73**:815 (Sept. 13) 1919.

reactions in Drinker and Brittingham's series with citrated blood. The technic of giving citrated blood is more simple, and this is its chief advantage. Unger reports a professional donor in New York who during six and a half years underwent sixty transfusions, donating thus about 50,000 c.c. of blood. He had lost his total blood volume ten times during this period. His hemoglobin percentage, taken nine weeks after his last transfusion, was 70 per cent., otherwise he was in perfect health.

Unger recommends an average dose of whole blood for infants, of from 80 to 150 c.c.; for adults, from 800 to 1,000 c.c. If overtransfusion takes place, the patient may develop pulmonary edema and die. A short, sharp cough is always a danger sign, and more than 200 c.c. should never be given after this occurs.

Hemophilia is not cured by transfusion, but for the bleeding, transfusion is practically a specific. In purpura hemorrhagica the results are only fairly good, and repeated transfusions are often necessary to control the bleeding. In acute lymphatic leukemia only a temporary favorable effect is secured. In hemorrhagic disease of the new-born, transfusion is specific and often a life saving procedure. In this condition, if hemorrhage from the gastro-intestinal tract occurs, no matter how small it may be, transfusion should be done at once without trying subcutaneous injections of whole blood, which, however, may be effective in hemorrhage from less important sites.

Garbat [43] recommends the citrate method. He collects the blood in two large measuring beakers and then filters it through gauze directly into an infusion flask from which it is allowed to run into the vein of the patient.

In 100 transfusions, 48 per cent. of subjects had no reaction at all, and 10 per cent. had a very slight reaction. A definite reaction occurred in 42 per cent., consisting of chilly sensations or chills, with fever and vomiting in the more severe cases.

A few reactions may be very severe, but do not do permanent harm to the patient. One must be absolutely certain that no clots form in the citrated blood, and to obviate this the mixture of blood and citrate is very thoroughly stirred and then filtered through gauze. If a 0.3 per cent. solution of citrate is used instead of the usual 0.2 per cent. solution, clots are much less likely to form.

---

43. Garbat, A. L.: Sodium Citrate Transfusions, J. A. M. A. **72**:1 (Jan. 4) 1919.